Ruthenium- and Palladium-Catalyzed Carbon-Carbon Bond Formation in Natural Product Synthesis

Jensen, Thomas

Publication date:
2009

Document Version
Publisher's PDF, also known as Version of record

Ruthenium- and Palladium-Catalyzed Carbon-Carbon Bond Formation in Natural Product Synthesis

Ph.D. Dissertation

Thomas Jensen
July 2009

Preface

The present dissertation is submitted in partial fulfillment of the requirements for the Ph.D. degree from the Technical University of Denmark (DTU). The work presented herein has been conducted both at the Department of Chemistry, DTU and during a nine months external stay in the Stoltz group at the California Institute of Technology (Caltech).

The dissertation is divided into six chapters (excluding appendices etc.) detailing subjects related to the intertwined fields of method development and organic synthesis. Chapters one to four are concerned with projects conducted at DTU, while chapter five describes work carried out at Caltech. Finally, chapter six provides a brief summary. The chapters can be read independently, however, the first chapter describing previous synthetic efforts toward (+)-castanospermine can be read as a prelude to chapter two featuring our synthetic endeavors on (+)-castanospermine. Chapter three provides a brief introduction to natural product inspired drug discovery, covers the biology of pladienolide B, and details our development of a synthetic strategy to the macrocyclic core of (−)-pladienolide B. Chapter four is concerned with the development of a ruthenium-catalyzed method to alkylate the 3-position of oxindoles. Chapter five describes our studies toward an asymmetric total synthesis of the sesterterpenoid variecolin.

Several people have had a significant impact on the projects described in this dissertation. First I would like to express my gratitude to my supervisor Professor Robert Madsen for always taking the time to in-depth discussions, and for his careful guidance on both practical and theoretical aspects of organic chemistry. Dr. Morten Jørgensen is also gratefully acknowledged for introducing me to the techniques of method development in transition-metal catalyzed organic reactions, and for giving me great advice over the years. Additionally, I would like to thank Dr. Philip R Skaanderup for providing me with an opportunity to work on the pladienolides and for his support through out critical stages of the project. Special thanks go to Johan H. Dam for sharing the lab, for numerous discussions on mechanistic problems and the latest developments in chemistry, and for great company. Assistant Professor Peter Fristrup is thanked for great collaborations and for the occasional burger at Hamburger Hamlet during the Caltech times. Finally, the entire Madsen group, as well as people at the Department of Chemistry building 201, is acknowledged for invaluable help and for creating a great working atmosphere.

At Caltech working under Professor Brian M. Stoltz's supervision was a tremendous privilege and pleasure. His passion and enthusiasm for chemistry is truly contagious. It was extremely inspiring to be part of one of the best research groups in the world. I was fortunate enough to spend almost nine month in his research laboratories, and I am very excited about being granted the opportunity to return as a postdoctoral scholar. I would like to thank first and foremost Michael R. Krout a very gifted chemist and great guy, who was my partner on the variecolin project. The entire Stoltz group is thanked for making the stay memorable and fruitful. I really enjoyed sharing the lab with Jenn Stockdill and Dave Ebner who became great friends and made sure that I got to see other sites than the Stoltz laboratories. Special thanks are also due to the Chemistry Department soccer team for great friendship and excellent matches in the intermurial cup.

I would like to express my thanks to Ph.D. student Johan H. Dam, Dr. Flemming G. Hansen, Dr. Rune N. Monrad, Dr. Katja Rohr-Gaubert, and Ph.D. student Michael R. Krout for carefully proofreading parts of this dissertation. Of course, any errors or omissions that may remain are the sole responsibility of the author.

The generous support from the Danish National Research Foundation in the form of an "EliteForsk-rejsestipendium" for my external stay at Caltech is greatly acknowledged. Finally, I would like to thank the Technical University of Denmark for a Ph.D. grant.

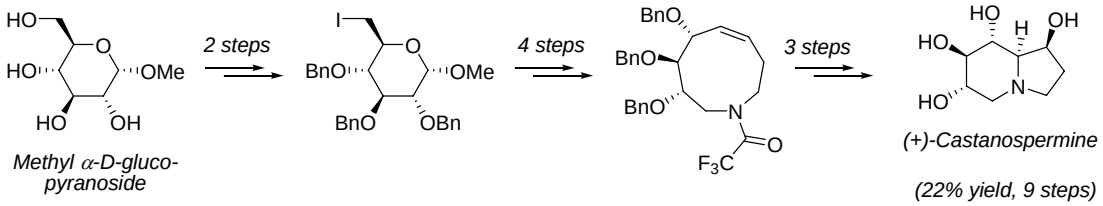
A special thanks goes to Marie and Christian for their great support and for being patient company during the preparation of this thesis.

Thomas Jensen

Kgs. Lyngby, July 2009

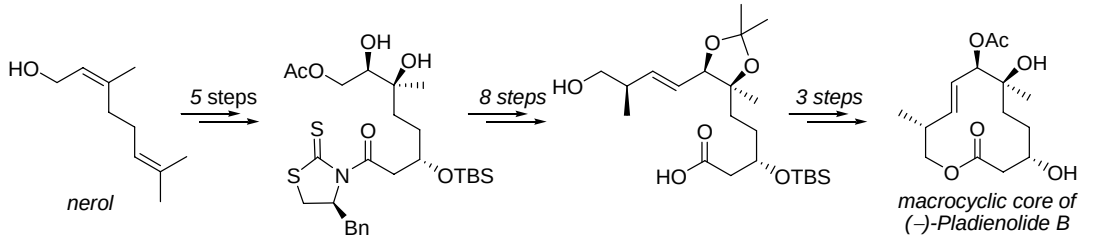
Abstract

Project 1: The Total Synthesis of (+)-Castanospermine



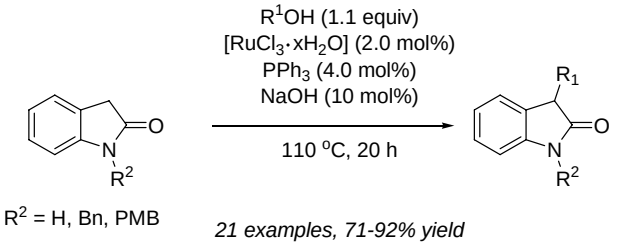
A novel synthesis of (+)-castanospermine has been achieved starting from methyl α-D-glucopyranoside. The powerful α- and β-glucosidase inhibitor was synthesized in 9 steps with 22% overall yield, which constitutes the shortest chiral pool approach to this target. The octahydroindolizidine skeleton of (+)-castanospermine was constructed by the sequential use of a medium ring metathesis reaction, a diastereoselective epoxidation, and a strain-releasing transannular cyclization. The prerequisite diene was available from a zinc-mediated reductive fragmentation of methyl 6-deoxy-6-iodo-α-D-glucopyranoside followed by reductive amination.

Project 2: Synthesis of the Macrocyclic Core of (−)-Pladienolide B



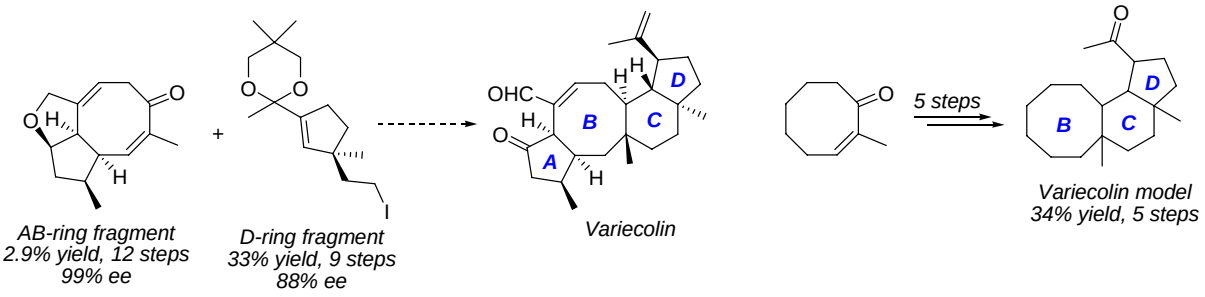
An efficient synthesis of the macrocyclic core of (−)-pladienolide B was achieved. The concise route relied on chiral auxiliary-mediated asymmetric aldol addition and Sharpless asymmetric dihydroxylation to install the three oxygen substituted stereocenters of the macrocycle. (*E*)-Selective cross metathesis followed by Yamaguchi-macrolactonization was implemented to install the 12-membered lactone and orthoester ring-opening was strategically applied to complete the synthesis. This purely reagent controlled and flexible strategy provides an excellent starting point for analog syntheses and structure activity relationship plotting of the appealing anticancer lead structure pladienolide B.

Project 3: Ruthenium-Catalyzed 3-Alkylation of Oxindoles



A highly efficient protocol based on a hydrogen autotransfer process to directly alkylate the C(3) position of oxindole utilizing alcohols has been developed. The reaction required in general 2.0 mol% of [$RuCl_3 \cdot xH_2O$], 4.0 mol% PPh_3 and 10 mol% sodium hydroxide to afford full conversion at 110 ^oC under neat reaction conditions. Importantly, this reaction provides a simple and highly atom-economical protocol to alkylate oxindoles. The reaction was highly selective for the formation of C(3) substituted oxindoles. This transformation was tolerant toward a relatively wide range of functional groups and could be applied to *o*-, *m*-, and *p*-substituted benzyl alcohols, several aromatic heterocycles, primary and secondary aliphatic alcohols.

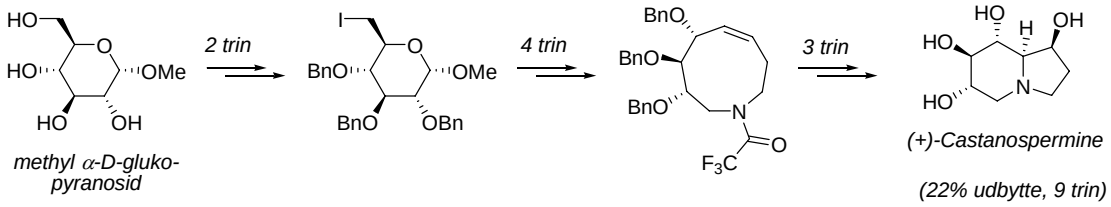
Project 4: Studies Toward the Asymmetric Total Synthesis of Variecolin



Efficient synthetic routes to an enantiopure AB-ring fragment and an enantioenriched D-ring fragment for the total synthesis of the sesterterpenoid variecolin has been developed. The central eight-membered ring of the AB fragment was constructed implementing the tandem Wolff-Cope rearrangement. Synthesis of the D-ring fragment was achieved utilizing the enantioselective decarboxylative allylation to construct the all-carbon quaternary stereocenter and a retro-aldol-aldol ring contraction to form the five-membered ring. Synthetic studies on the late stage coupling of a model AB-ring fragment and the D-ring fragment have revealed that these fragments can be convergently combined through a 1,4-hydrosilylation-alkylation sequence followed by conjugate radical cyclization.

Danish Abstract

Projekt 1: Totalsyntese af (+)-Castanospermine



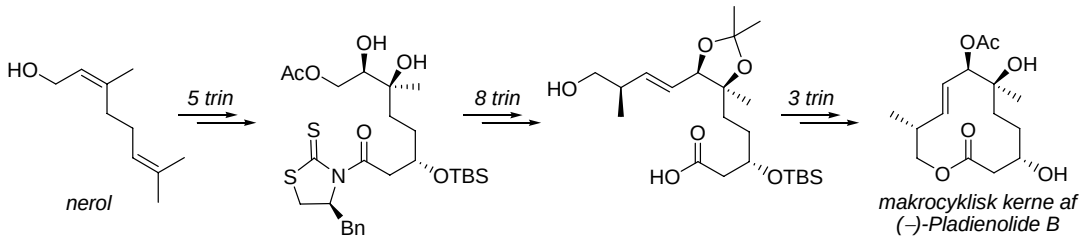
methyl α-D-gluko-pyranosid

(+)-Castanospermine

(22% udbytte, 9 trin)

En ny syntese til fremstilling af (+)-castanospermine med methyl α-D-glukopyranosid som udgangsstof er blevet udviklet. Denne potente α- og β-glukosidase inhibitor er blevet syntetiseret i 9 trin og 22% overordnet udbytte, hvilket udgør den hidtil korteste syntese af (+)-castanospermine startende fra chiralt materiale. Octahydroindolizidinskellet af (+)-castanospermine blev bygget vha. medium ringslutningsmetatese, diastereoselektiv epoxidering og transannular cyklisering. Dienen til ringslutningsmetatesen blev fremstillet vha. zink-medieret reduktiv fragmentering af methyl 6-deoxy-6-iod-α-D-glukopyranosid og efterfølgende reduktiv aminering.

Projekt 2: Syntese af den Makrocykliske Kerne af (−)-Pladienolide B



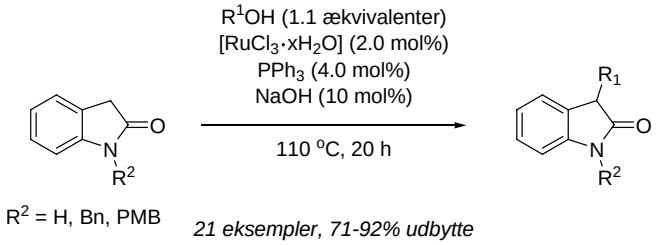
nerol

makrocyklisk kerne af (−)-Pladienolide B

(6.5% udbytte, 16 trin)

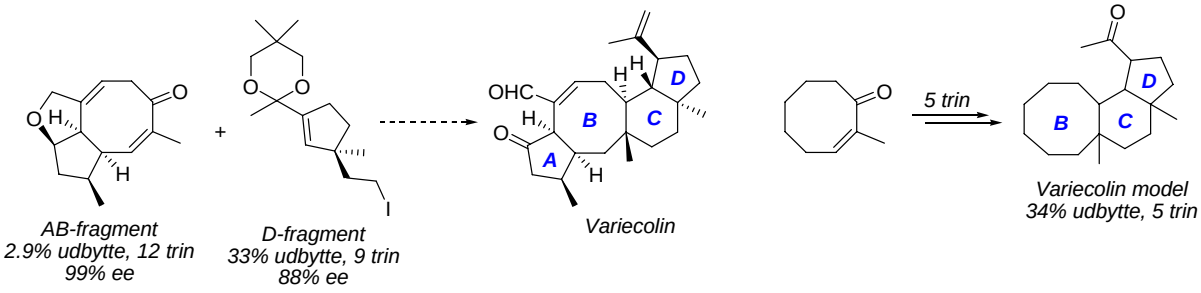
En effektiv syntese af den makrocyklisk kerne af (−)-pladienolide B er blevet udviklet. Syntesen anvendte en auxiliary-medieret asymmetrisk aldolkondensation og Sharpless asymmetrisk dihydroxylering til at installere de tre oxygen-substituerede stereocentre på makrocyklen. (*E*)-Selektiv krydsmetatese efterfulgt af Yamaguchi-makrolaktonisering blev benyttet til at konstruere den 12-leddede lakton, og endelig blev regioselektiv ortho-ester-åbning anvendt til at fuldføre syntesen. Denne reagens-kontrollerede og fleksible syntesestrategi udgør et glimrende udgangspunkt for syntese af analoger og struktur-aktivitets studier af det lovende anticancerstof pladienolide B.

Projekt 3: Ruthenium-Katalyseret 3-Alkylering af Oxindoler



En effektiv ny metode til at alkylere C(3)-positionen af oxindoler baseret på overgangsmetal-katallyseret hydrogenoverførsel er blevet udviklet. Generelt krævede reaktionen 2.0 mol% [$RuCl_3 \cdot xH_2O$], 4.0 mol% PPh_3 og 10 mol% natriumhydroxid for at opnå fuld omsætning. Reaktionen udgør en simple og atomøkonomisk metode til at alkylere oxindoler. Denne reaktion er kompatibel med en relativt bred vifte af funktionelle grupper og kunne udføres med *o*-, *m*-, og *p*-substituerede benzylalkoholer, adskillige heteroaromatiske alcoholer, samt primære og sekundære alifatiske alkoholer.

Projekt 4: Syntesestudier mod en Asymmetrisk Totalsyntese af Variecolin



Der er blevet udviklet effektive synteseveje til et enantiomerisk rent AB-fragment og et D-fragment beriget i den ene enantiomer, som en del af totalsyntesen imod sesterterpenoidet variecolin. Den centrale otte-leddede ring i AB-fragmentet blev bygget vha. en tandem Wolff-Cope-omlejring. Syntesen af D-fragmentet blev gennemført ved brug af en enantioselektiv decarboxylativ allylering til at installere det kvarternære stereocenter og en retro-aldol-aldol sekvens til at danne den fem-leddede ring. Studier af koblingen mellem en model for AB-fragmentet og D-fragmentet viste, at disse kunne kombineres konvergent ved anvendelse af en 1,4-hydrosilylering-alkyleringssekevens, efterfulgt af en konjugeret radikalcyklisering

Publications

Papers Included in the Dissertation

1) *"Synthesis of the Macrocyclic Core of (–)-Pladienolide B"* Philip R. Skaanderup and Thomas Jensen *Org. Lett.* **2008**, *10*, 2821.

2) *"Ruthenium-Catalyzed Alkylation of Oxindole with Alcohols"* Thomas Jensen and Robert Madsen *J. Org. Chem* **2009**, *74*, 3990.

3) *"A Concise Synthesis of Castanospermine by the Use of a Transannular Cyclization"* Thomas Jensen, Mette Mikkelsen, Thomas L. Andresen, Anne Lauritsen, and Robert Madsen *J. Org. Chem.* **2009** (in preparation).

Additionally, the literature described in chapter 1 and the work described in chapter 3 is currently being converted into a review and a full paper, respectively.

Papers Not Included in the Dissertation

The research described in the following scientific publications includes work completed during the Ph.D. study, which has not been included in the final dissertation.

4) "*Palladium-Catalyzed Aryl Amination-Heck Cyclization Cascade: A One-Flask Approach to 3-Substituted Indoles"* Thomas Jensen, Henrik Pedersen, Benny Bang-Andersen, Robert Madsen, and Morten Jørgensen *Angew. Chem. Int. Ed.* **2008**, *47*, 888.

5) *"Oxidation of Amines with Molecular Oxygen Using Bifunctional Gold-Titania Catalysts"* Søren K. Klitgaard, Kresten Egeblad, Uffe V. Mentzel, Andrey G. Popov, Thomas Jensen, Esben Taarning, Inger S. Nielsen, and Claus H. Christensen *Green Chem.* **2008**, *10*, 419.

Table of Contents

1 Biology and Synthetic Approaches to (+)-Castanospermine

Due to its highly interesting biological profile and intriguing structural complexity, (+)-castanospermine has been the subject of numerous total syntheses since the original isolation in 1981. These syntheses commence from either a carbohydrate,[1-13] tartaric/malic acid[14-16] or an achiral material employing an enantioselective strategy.[17-22] The synthetic approaches to stereoisomers and analogs of (+)-castanospermine before 1996 have been subject to excellent reviews by Burgess and Henderson[23] and Tyler and Winchester.[24] Later approaches have been summarized in general reviews on indolizidine and quinolizidine alkaloids by Michael.[25-36] Therefore the scope of the present chapter is to provide an overview of the syntheses reported since 1996 focusing exclusively on approaches to (+)-castanospermine. Moreover, the purpose of this review is to provide a brief introduction to the biology of (+)-castanospermine and to analyze the syntheses critically in a chronological order with particular focus on how the characteristic indolizidine skeleton was constructed. Initially, "chiral pool" syntheses starting from carbohydrates will be analyzed, and then syntheses starting from (–)-malic acid. Finally, this review describes the enantioselective syntheses starting from achiral materials.

1.1 Isolation and Biological Background

(+)-Castanospermine (**1.1**) was first isolated in 1981 from the seeds of the Moreton Bay chestnut *Castanospermum australe* by Hohenschutz and co-workers[37] and later from the dry pods of *Alexa leiopetala*.[38] In the original report, the absolute stereochemistry of (+)-castanospermine (**1.1**) was arbitrarily chosen as one enantiomer, however, the total synthesis by Ganem and Bernotas[1] unambiguously established the absolute stereochemistry as depicted in **1.1**. (+)-Castanospermine (**1.1**) belongs to a family of naturally occurring polyhydroxylated indolizidine alkaloids (Figure 1.1)

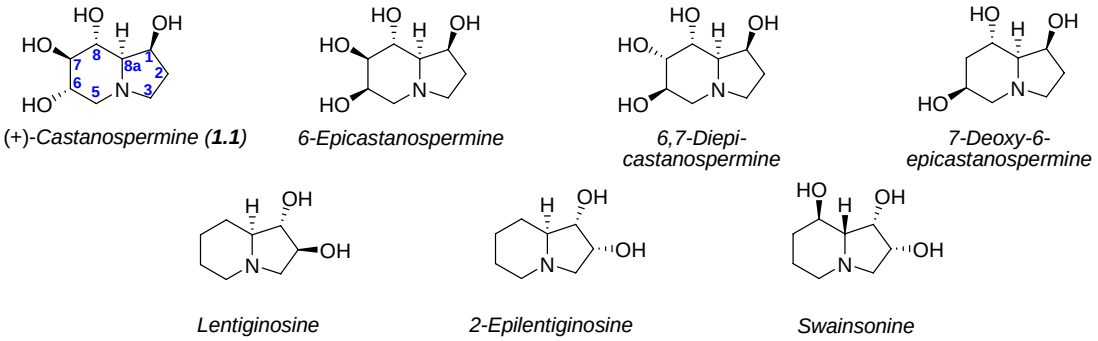
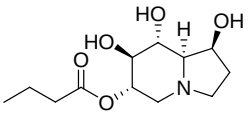


Figure 1.1 A selection of naturally occurring indolizidine alkaloids.

(+)-Castanospermine (**1.1**) has been shown to be a potent inhibitor of several glycosidases.[39-41] Furthermore, studies have demonstrated that (+)-castanospermine (**1.1**) has potential for treatment of viral infections,[42] various cancer types,[43] and diabetes.[44] Additionally, **1.1** has displayed anti-inflammatory[45] and immunosuppressant properties.[46] The source of this remarkable plethora of biological activity has been ascribed to (+)-castanospermine's glycosidase inhibitory properties. Glycosidases are enzymes recruited to catalyze the hydrolysis of glycosidic bonds. The hydrolysis of glycosidic bonds is of crucial importance, since many fundamental processes are governed by carbohydrate-mediated information *e.g.* quality control of protein folding, modulation of cell-cell adhesion, and signalling.[47]

Recent studies have revealed that (+)-castanospermine (**1.1**) is a potent inhibitor of dengue virus infection *in vitro* and *in vivo*. Importantly, Diamond and co-workers[48] demonstrated that **1.1** prevented mortality in mice infected with dengue virus, and *in vitro* studies showed that all four serotypes of dengue virus were inhibited. It is believed that **1.1** inhibits the viral infection by disrupting the folding of several viral proteins of structural importance. This has been ascribed to (+)-castanospermine's ability to prevent removal of terminal glucose residues on *N*-linked oligosaccharides, which may interrupt interaction with protein folding enzymes.[49]

In 2004 (+)-castanospermine (**1.1**) and the ester derivative celgosivir (**1.2**) were tested as treatment for hepatitis C virus (HCV), the major cause of acute hepatitis and chronic liver disease (Figure 1.2). Utilizing a plague assay and a cytopathic effect assay Whitby and co-workers[50] found that celgosivir (IC_{50} = 16 and 47 μm, respectively) was a more potent inhibitor than (+)-castanospermine (**1.1**) (IC_{50} = 110 and 367 μm, respectively). Currently, celgosivir in combination with interferon-α and ribavirin (two licensed agents for treatment of HCV) is undergoing phase II clinical trials.[51]



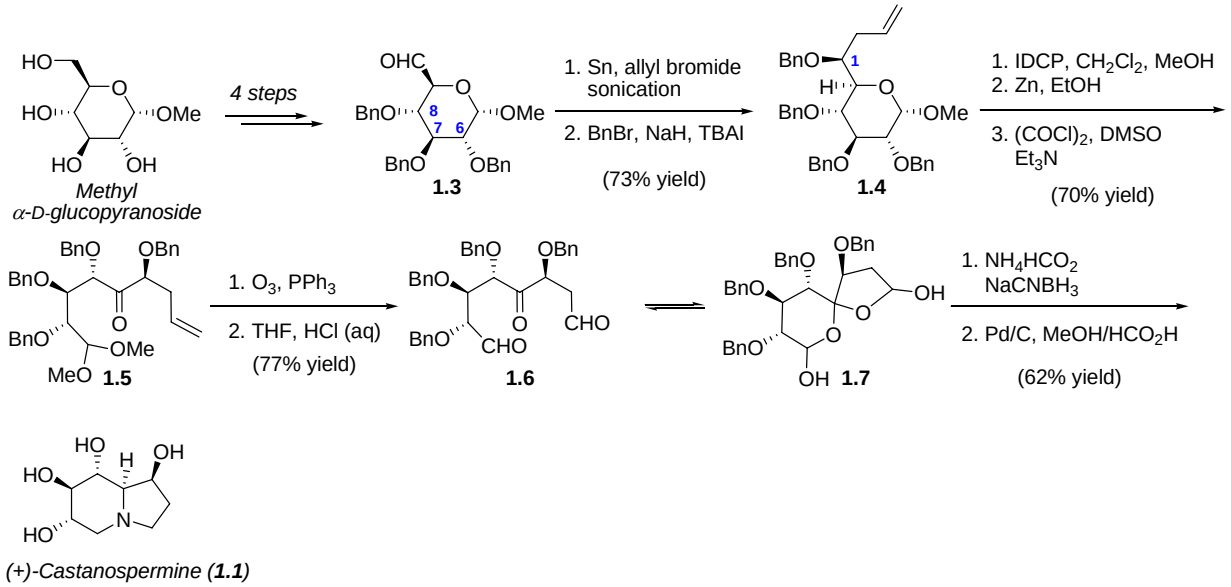
*Celgosivir (**1.2**)*

Figure 1.2 (+)-Castanospermine derivative in phase II clinical trials for treatment of chronic HCV.

1.2 Syntheses of (+)-Castanospermine from Carbohydrate Starting Materials

1.2.1 Mootoo's Approach

In a preliminary communication in 1996 and a full paper in 2001, Mootoo and co-workers[9,52] described the total synthesis of (+)-castanospermine starting from aldehyde **1.3** which is available in 4 steps from methyl α-D-glucopyranoside (Scheme 1.1). The octahydroindolizidine skeleton of (+)-castanospermine was effectively constructed using a triple reductive amination cascade. The stereocenters at C(6), C(7), and C(8) were all derived from methyl α-D-glucopyranoside, while the stereocenter at C(1) was forged using a tin-mediated allylation under Barbier conditions.



Scheme 1.1 Mootoo's reductive amination approach to **1.1**.

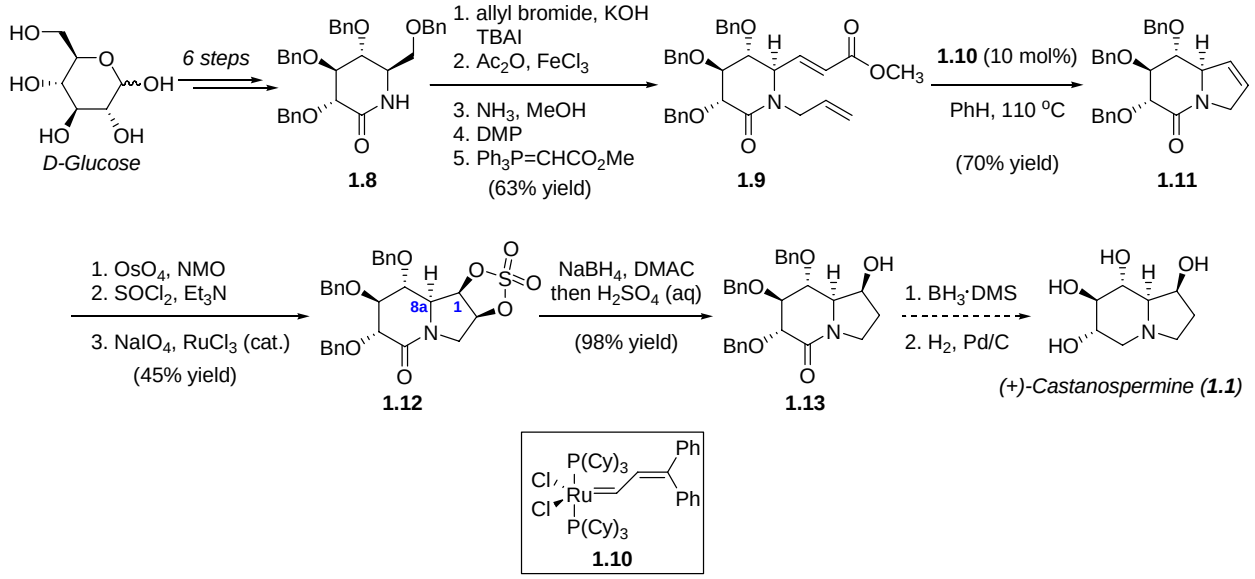
Aldehyde **1.3** was treated with allyl bromide and tin metal under conditions developed by Whitesides[53] affording the requisite allylated pyranoside **1.4** upon benzyl ether protection.[a] When **1.4** was treated with iodonium dicollidine perchlorate (IDCP), a mixture of iodo-tetrahydrofurans was obtained,[54] which upon exposure to zinc metal and subsequent Swern oxidation afforded methoxy acetal **1.5**. Ozonolytic cleavage and acetal hydrolysis provided the tricarbonyl species **1.6** existing as a mixture of lactol isomers **1.7**. Fortunately, treating **1.7** with ammonium formate and sodium cyanoborohydride followed by global deprotection afforded **1.1** in good yield. The high stereoselectivity observed during the reductive amination can be ascribed to preferential α-face

[a] The allylation led to a 9:1 mixture of alcohol epimers, these were easily separated using silica-gel chromatography.

hydride delivery on putative mono- or bicyclic iminium ion intermediates. In summary, the synthesis of **1.1** took place in 9 steps from aldehyde **1.3** with an overall yield of 25% yield. The key to this successful and concise synthesis was the realization of a triple reductive amination cascade providing the entire indolizidine skeleton in one-pot.

1.2.2 Pandit's Approach

As part of a research program directed toward the synthesis of bicyclic azasugars, Pandit and co-workers[55,56] developed an efficient synthetic route to monocyclic sugar lactams such as **1.8** derived from D-glucose (Scheme 1.2). In 1996 this material served as platform for Overkleeft and Pandit's formal total synthesis of **1.1**.[8] Having already the six-membered moiety of the indolizidine skeleton in place, Pandit sought to implement a ring-closing metathesis strategy to forge the five-membered ring onto the sugar lactam **1.8**. The stereogenic center at C(1) was build utilizing a diastereoselective dihydroxylation.



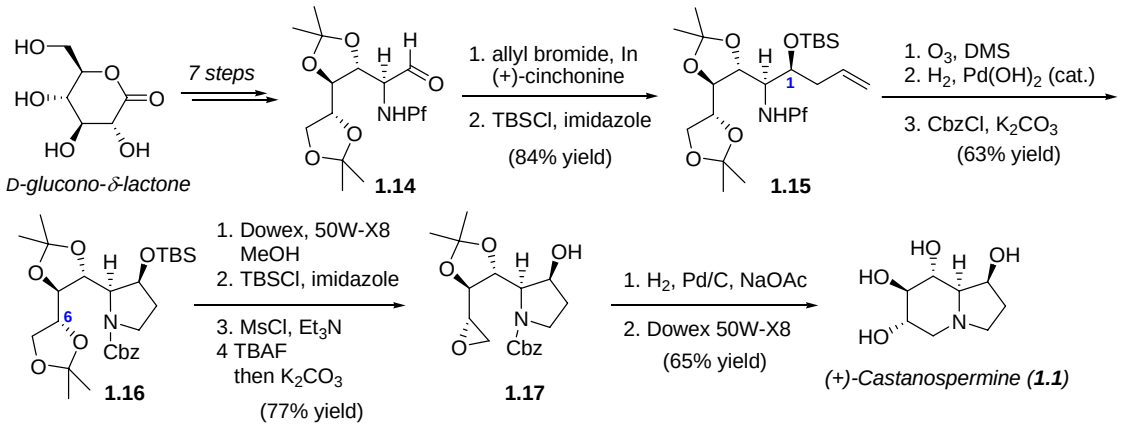
Scheme 1.2 Pandit's formal total synthesis of **1.1**.

Lactam **1.8** was transformed into the RCM precursor **1.9** through a five step sequence. This diene was treated with the ruthenium carbene catalyst **1.10** developed by Grubbs[57] affording the desired bicyclic lactam **1.11** in good yield. *En route* to the formal total synthesis, the newly formed double bond was oxidized using osmium tetraoxide and *N*-methylmorpholine *N*-oxide affording a diastereomeric mixture of diols. This mixture was converted into cyclic sulphates via the corresponding sulphites. Separation of these sulphates provided the desired product **1.12** in 45%

yield along with 9% of the undesired diastereomer (not shown). While the authors did not provide an explanation for the stereochemical outcome, it seems reasonable that the C(8a) proton disfavors attack at the α-face of the bicyclic lactam due to steric interactions. The resulting sulphate was exposed to sodium borohydride which upon hydrolysis gave lactam **1.13**. The exquisite regioselectivity of the nucleophilic attack was ascribed to exclusive attack at the sterically least congested site. In summary, Pandit has provided a formal total synthesis of **1.1** affording lactam **1.13** in 11 steps from **1.8** in a 19% overall yield.

1.2.3 Park's Approach

In 2003 Park and co-workers[10] disclosed a total synthesis of **1.1** commencing from aminoaldehyde **1.14** which is available from D-glucono-δ-lactone using methodology developed by the laboratories of Vasella[58] and Rapoport[59] (Scheme 1.3). With **1.14** as entry point for their synthesis, the stereogenic centers at C(7), C(8), and C(8a) were already installed with the correct absolute configuration, whereas the C(6) stereocenter had to be inverted. Diastereoselective indium-mediated allylation was recruited to provide the final stereocenter at C(1). The indolizidine system was build in two separate steps employing intramolecular reductive amination to build the five-membered ring, and similar to Kang's approach (cf. chapter 1.3.1) a strain-releasing cyclization of epoxide **1.17** was deployed to append the six-membered ring.



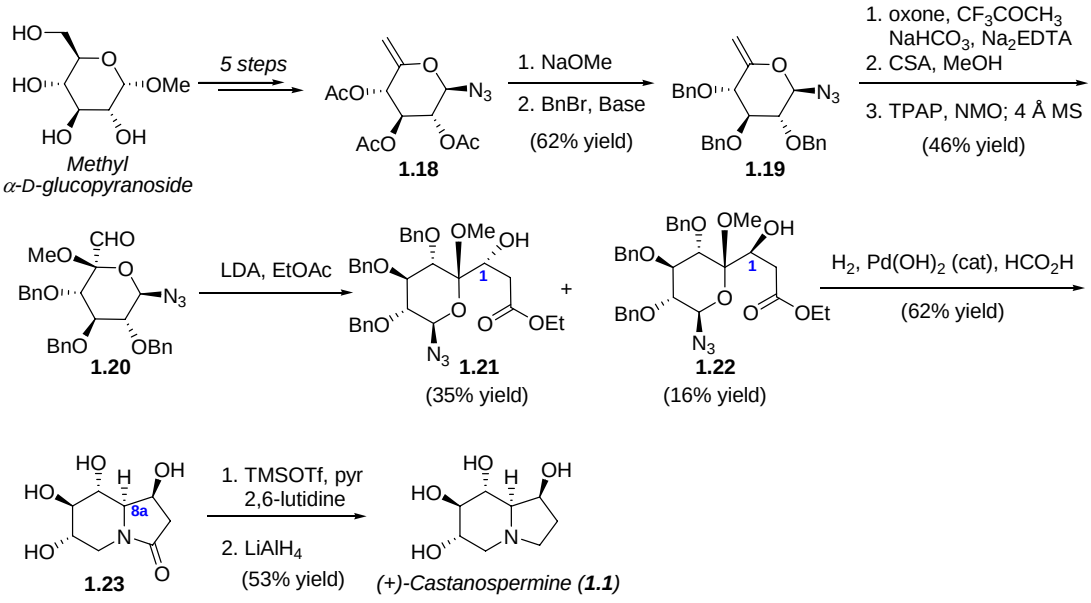
Scheme 1.3 Park's total synthesis of **1.1**.

When aldehyde **1.14** was treated with a preformed allylindium reagent in the presence of (+)-cinchonine at low temperature, **1.15** was smoothly obtained after TBS-protection. The allylation almost exclusively provided the desired diastereomer (*dr* = 50:1). This exquisite *syn* diastereo-

selectivity can be explained invoking the chelation control model described by Cram.[60] Ozonolysis of the terminal alkene followed by catalytic hydrogenation facilitated one-carbon shortening, deprotection and cyclization. After Cbz-protection, the desired pyrrolidine **1.16** was obtained in good yield. A deprotection-protection sequence followed by mesylation and silylether cleavage furnished epoxide **1.17**. Hydrogenolysis of the *N*-Cbz protecting group was accompanied by ring-closure to a protected indolizidine, which upon exposure to an acidic ion-exchange resin gave **1.1**. To summarize, Park attained the total synthesis of **1.1** in 11 steps and 26% overall yield starting from aminoaldehyde **1.14**.

1.2.4 Murphy's Approach

In 2005 Cronin and Murphy[11] disclosed a total synthesis of (+)-castanospermine (**1.1**) commencing from azide **1.18**,[61,62] which is available in five steps from methyl α-D-glucopyranoside (Scheme 1.4). The central features of the synthesis were incorporation of an aldol reaction to afford the C(1) stereogenic center and a reductive amination cascade to generate the indolizidine ring system and concomitantly provide the correct stereochemistry at C(8a).



Scheme 1.4 Murphy's total synthesis of **1.1**.

Initially, the alkene **1.19** was generated from azide **1.18**. Subsequent epoxidation, acid induced methanolysis and Ley oxidation afforded aldehyde **1.20** in 46% yield along with 12% of the epimer (not shown). When aldehyde **1.20** was condensed with the lithium enolate of ethyl acetate the β-

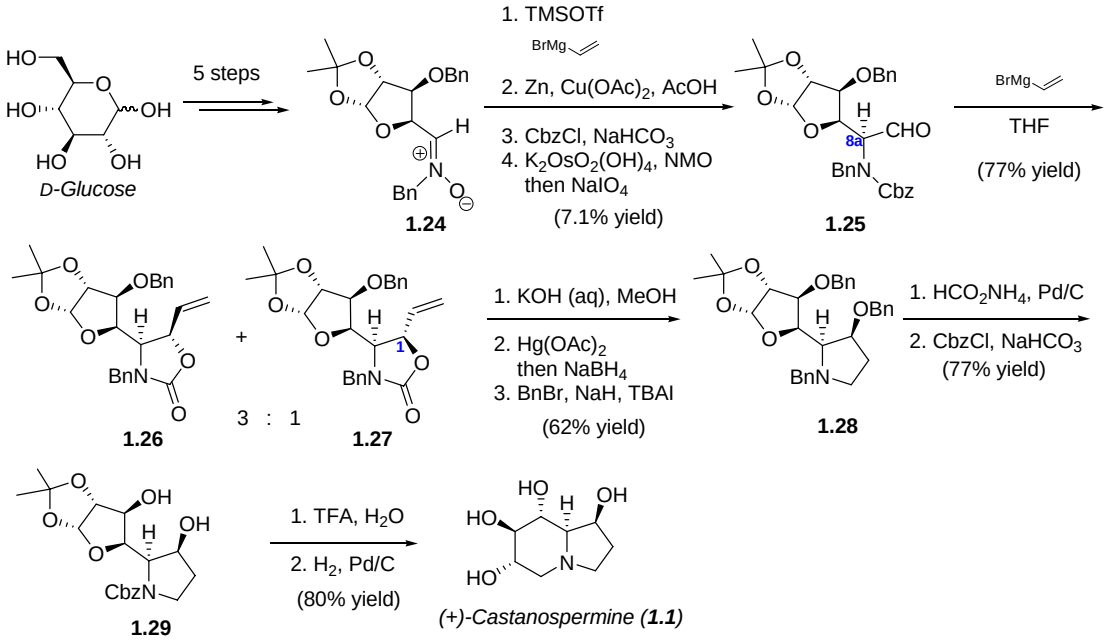
hydroxy esters **1.21** and **1.22** were obtained in 35% and 16% yield, respectively. The minor isomer **1.22** was carried on to the key amination cascade, which was mediated by hydrogenation over Pearlman's catalyst. The cascade involved reduction of the azide moiety, intramolecular reductive amination, debenzylation, and lactam formation providing **1.23** in 62% yield. Furthermore the cascade succeeded in installing the correct bridgehead stereochemistry for the target alkaloid. (+)-Castanospermine (**1.1**) was obtained from **1.23** via silylation of the free alcohol followed by reduction and acidic work-up. In summary, Cronin and Murphy have accessed **1.1** in 9 steps with a 1.5% overall yield starting from azide **1.18**. The relatively low overall yield was primarily caused by poor selectivity in the aldol reaction, however, the undesired (major) diastereomer from this step could be funneled into a synthesis of 1-*epi*castanospermine.

1.2.5 Dhavale's Approach

In 1997 Dhavale and co-workers[63,64] revealed interest in azasugars exploiting sugar-derived nitrones as starting point for their synthetic endeavors. Nine years later, in 2006, these explorations culminated in the total synthesis of (+)-castanospermine (**1.1**).[12] The synthesis initiated from nitrone **1.24** which is available in 5 steps from D-glucose (Scheme 1.5).[63,65,66] Three of the five stereocenters were attained from D-glucose, while the stereocenters at C(8a) and C(1) were installed using diastereoselective vinylmagnesium bromide addition. The octahydroindolizidine skeleton was constructed through a mercury-mediated *5-endo-trig* cyclization and an intramolecular reductive amination.

The synthesis commenced with vinylmagnesium bromide addition to nitrone **1.24** in the presence of trimethylsilyl triflate. Two separable isomers were formed in a 13:87 ratio, and the major diastereomer was converted into aldehyde **1.25** through an additional three steps. The observed selectivity could be explained by invoking the Felkin-Anh selectivity model.[67,68] A second vinylmagnesium bromide addition afforded a diastereomeric mixture of two vinyloxazolidinones **1.26** and **1.27** in a 3:1 ratio. Unfortunately, it was the minor isomer **1.27** that possessed the requisite stereochemistry. However, the major isomer could be applied in a total synthesis of 1-*epi*-castanospermine. Again the selectivity was explained in terms of Felkin-Anh-like transition states. Hydrolysis of the minor product **1.27** followed by an aminomercuration-demercuration sequence and benzyl protection furnished **1.28** in good yield. Hydrogenolysis of the three benzyl groups

followed by Cbz-protection of the amine afforded **1.29**, which was poised to undergo intramolecular reductive amination to construct the six-membered ring of **1.1**.

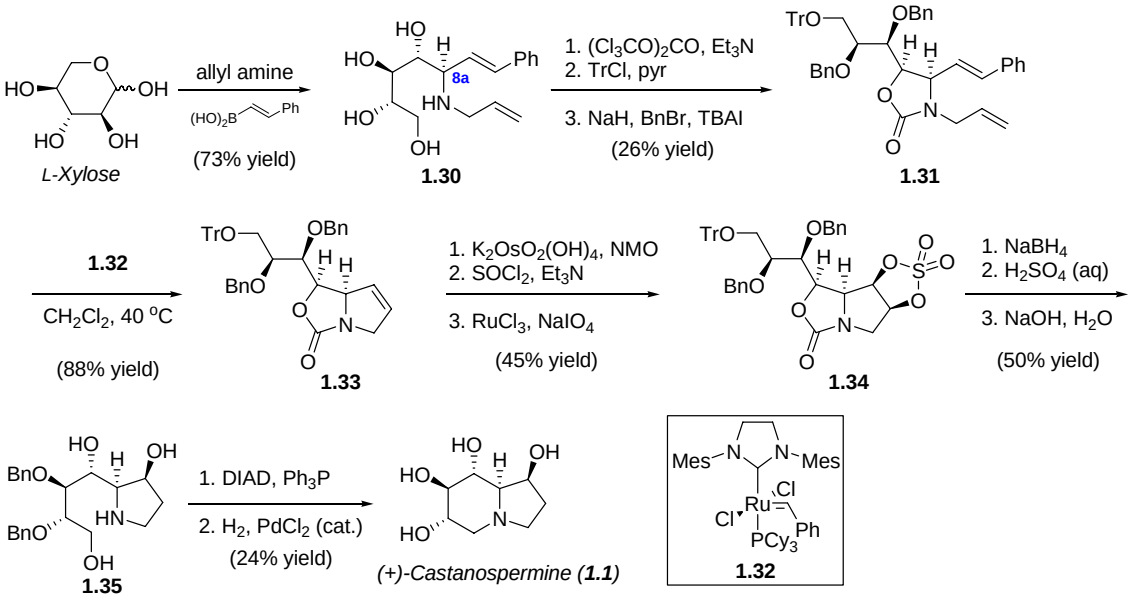


Scheme 1.5 Dhavale's nitrone based approach to **1.1**.

Ultimately, deprotection of the acetonide functionality utilizing trifluoroacetic acid and water followed by hydrogenation over palladium on charcoal gave (+)-castanospermine (**1.1**) in excellent yield. To summarize, Dhavale has obtained access to **1.1** in 0.68% overall yield in 12 steps. The relatively low overall yield was primarily caused by poor selectivity in the two vinylmagnesium bromide additions to **1.24** and **1.25**.

1.2.6 Pyne's Approach

In 2004 Pyne and co-workers disclosed a novel strategy for targeting indolizidine alkaloids.[69] Recently, this strategy relying on the diastereoselective Petasis borono-Mannich[70] reaction between L-xylose, allyl amine and (*E*)-styrene boronic acid has been implemented in the total synthesis of (+)-castanospermine (**1.1**) (Scheme 1.6).[13] The borono-Mannich reaction provided the correct stereochemistry at C(8a). The five-membered ring of the indolizidine skeleton was formed in analogy with Pandit's approach (cf. Chapter 1.2.2) using RCM, while the six-membered ring was constructed using a Mitsunobu displacement.



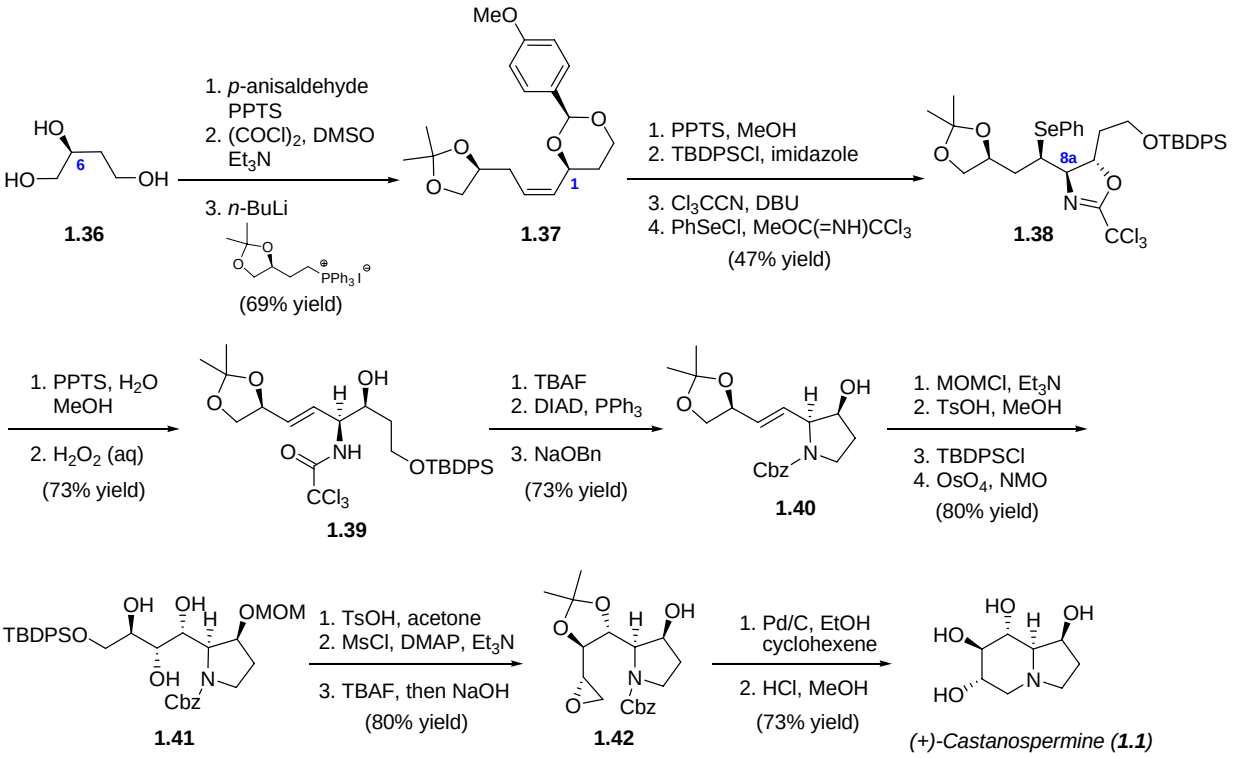
Scheme 1.6 Pyne's total synthesis of **1.1**.

The amino-tetraol **1.30** attained from the borono-Mannich reaction was converted into oxazolidin-2-one **1.31** by treatment with triphosgene under basic conditions and subsequent tritylation followed by benzylation. From intermediate **1.31**, the five-membered ring of the indolizidine structure was formed via ring-closing metathesis. *syn*-Dihydroxylation of **1.33** furnished the desired diol along with minor amounts of the undesired diastereomer resulting from α-face dihydroxylation. The diol was converted into sulphate **1.34**, which in analogy to Pandit's approach (cf. Chapter 1.2.2) afforded **1.35** upon regioselective reductive ring-opening of the cyclic sulphate and basic hydrolysis of the oxazolidinone ring. Triol **1.35** was subjected to Mitsunobu cyclization conditions affording the desired amine only in low yield due to competing cyclizations to the free hydroxy groups. Ultimately, debenzylation afforded **1.1** in 24% yield. In summary, Pyne have arrived at **1.1** in 11 steps from L-xylose and 0.9% overall yield. The synthesis rapidly constructs four of the five contiguous stereocenters of **1.1**, however, the overall efficiency is hampered by unselective protecting group manipulations and lack of control during the final cyclization.

1.3 Synthesis of (+)-Castanospermine from Malic Acid

1.3.1 Kang's Approach

In 1998 Kang and Kim[16] disclosed their total synthesis of **1.1**. Unlike the majority of the chiral pool approaches to (+)-castanospermine (**1.1**), Kang commenced the synthesis from the triol **1.36**, which is commercially available or can be synthesized in one step from L-(−)-malic acid (Scheme 1.7). The stereogenic centers at C(6) and C(1) were obtained from the chiral triol, whereas the remaining stereocenters were installed using a diastereoselective dihydroxylation and a phenylselenyl chloride-mediated cyclization. The five-membered ring of the octahydroindolizidine system was formed via an intramolecular Mitsunobu displacement, and the six-membered ring was constructed employing a strain-releasing 6-*endo* cyclization.



Scheme 1.7 Kang's malic acid based synthesis of **1.1**.

Triol **1.36** was transformed into diacetal **1.37** through reaction with *p*-anisaldehyde in the presence of PPTS, Swern oxidation, and Wittig olefination. The *p*-methoxybenzylidene group was chemoselectively hydrolyzed using PPTS in methanol. Subsequent regioselective silylether formation, treatment with 2,2,2-trichloacetimdate, and phenylselenyl chloride-mediated cyclization

favored the construction of *trans*-oxazoline **1.38** (*trans*:*cis* = 15:1). The high degree of stereocontrol during the cyclization was not addressed by the authors, however, a likely explanation is that the stereocenter at C(1) induces diastereoselectivity through minimization of $A^{1,3}$-strain.[71] Oxazoline **1.38** was partially hydrolyzed to the corresponding hydroxy trichloroacetamide, which upon oxidative elimination furnished **1.39**. Desilylation, Mitsunobu cyclization, and treatment with NaOBn afforded pyrrolidine **1.40**. Three standard protection group manipulations followed by a diastereoselective dihydroxylation gave triol **1.41** in high yield along with minor amounts of the isomeric triol (15:1 ratio). The observed diastereoselectivity was in accordance with selectivity models proposed by Kishi[72,73] and Stork.[74] After conversion into epoxide **1.42** removal of the Cbz-group induced 6-*endo* cyclization rather than 5-*exo* cyclization, this was attributed to the anti arrangement of the dioxolane ring. Ultimately, HCl-promoted methanolysis afforded **1.1**. In summary, Kang and Kim have attained **1.1** in 21 steps and 8.1% overall yield. A phenylselenyl chloride-mediated cyclization was employed to install the stereocenter at C(8a) constituting a novel solution to this synthetic challenge.

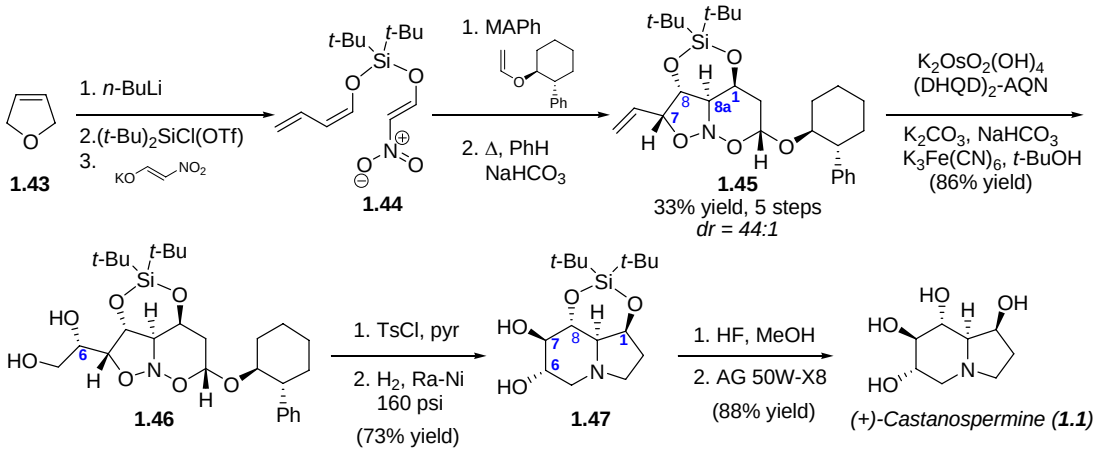
1.4 Enantioselective Syntheses of (+)-Castanospermine from Achiral Materials

1.4.1 Denmark's Approach

During the last part of the 1990's, Denmark and co-workers[75-80] investigated the tandem asymmetric [4 + 2]/[3 + 2] cycloaddition of nitroalkenes as a general method to synthesize pyrrolidine- and pyrrolizidine-containing compounds. In 1999 this tandem reaction was employed in the total synthesis of **1.1**. (Scheme 1.8)[19] A key intermediate in this approach was the nitroso acetal **1.45**, which also served as entry point to the total synthesis of (+)-6-*epi*castanospermine, (+)-australine and (+)-3-*epi*australine emphasizing the generality of this strategy. The tandem asymmetric [4 + 2]/[3 + 2] cycloaddition afforded four of the five contiguous stereocenters. The octahydro-indolizidine framework was assembled in one step combining hydrogenolytic unmasking of the nitroso acetal **1.46**, *N*-alkylation, and reductive amination.

The synthesis commenced by treating 2,5-dihydrofuran **1.43** with *n*-BuLi to afford a rapid ring-opening. Silylation of the ensuing lithium alkoxide using di-*tert*-butylchlorosilyl triflate followed by chloride displacement with potassium nitroacetaldehyde gave nitroalkene **1.44**. This species was

found to be intrinsically unstable losing the nitroalkene fragment when stored at room temperature or purified using conventional methods *i.e.* chromatography and distillation. Hence, Denmark and Martinborough decided to purify **1.44** using filtration through Celite. Extensive investigations revealed that the crucial [4 + 2]/[3 + 2] cycloaddition could be attained when **1.44** was treated with methylaluminum bis(2,6-diphenyloxide) (MAPh) and a chiral vinyl ether followed by heating. The desired product **1.45** arose from an *exo* [4 + 2] cycloaddition with excellent diastereofacial selectivity (44:1) and a [3 + 2] cycloaddition proceeding with exclusive *exo* selectivity and complete facial selectivity. The silaketal tether was believed to enforce the *exo* approach of the dipolarofile to the 1,3-dipole from the face to which the tether was attached.

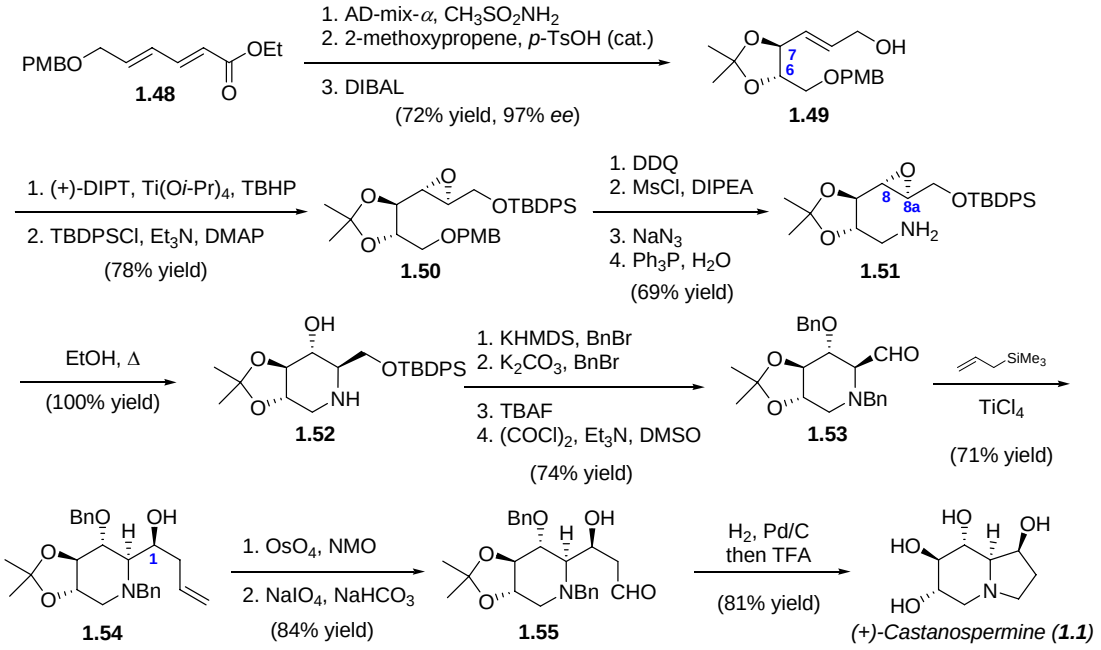


Scheme 1.8 Denmark's [4+2]/[3+2] cycloaddition approach to **1.1**.

The final hydroxylated stereogenic center at C(6) was introduced using Sharpless asymmetric dihydroxylation in the presence of an anthraquinone ligand $(DHQD)_2$-AQN. This ligand provided excellent diastereofacial selectivity, and **1.46** was obtained in 86% yield. With all stereogenic centers in place all that remained was formation of the bicyclic indolizidine structure. This was attained by activating the primary alcohol of **1.46** using selective tosylation and Raney-Ni catalyzed hydrogenolytic unmasking of the nitroso acetal. Ultimately, **1.1** was prepared by exposing the di-*tert*-butylsilylene **1.47** to HF in MeOH and subjecting the ensuing fluoride salt to cation-exchange chromatography. In summary, Denmark has synthesized **1.1** in 8 steps commencing from 2,5-dihydrofuran and 18% overall yield. This synthetic approach constitutes the shortest synthesis of **1.1** reported to date. Despite its initial lability, the silaketal functionality served to afford both excellent levels of diastereocontrol and to protect the C(8) and C(1) hydroxy groups.

1.4.2 Somfai's Approach

In 1998 Somfai[81] launched an approach toward polyhydroxylated alkaloids, *i.e.* aza-sugars, founded on enantioselective asymmetric catalysis. Later this strategy was successfully implemented in the total synthesis of **1.1** (Scheme 1.9). The six-membered ring of **1.1** was constructed through an intramolecular epoxide opening, whereas the five-membered ring was produced through intramolecular reductive amination. The stereogenic centers at C(6), C(7), C(8), and C(8a) were formed via the successive us of the Sharpless asymmetric dihydroxylation and epoxidation protocols, and the final stereocenter at C(1) was set using a Sakurai allylation.



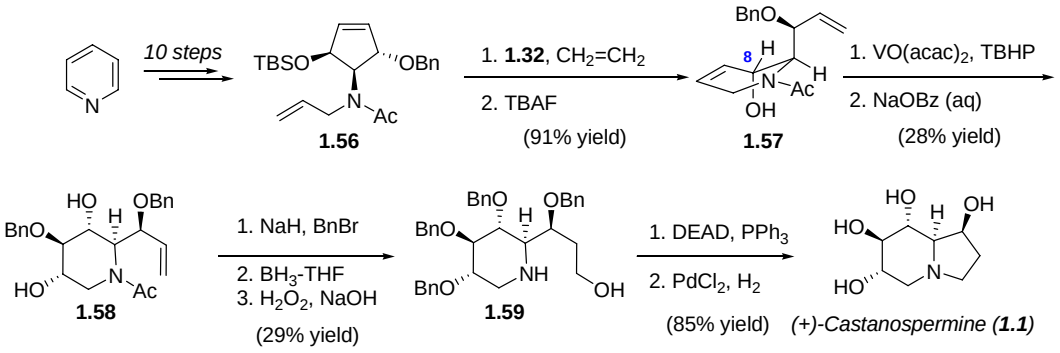
Scheme 1.9 Somfai's total synthesis of **1.1**.

Diene **1.48** was dihydroxylated with AD-mix-α and the resulting diol was protected as the corresponding acetonide and subsequently reduced using DIBAL to afford allylic alcohol **1.49** in 72% yield and 97% *ee*. Sharpless epoxidation of the protected **1.49** in the presence of stoichiometric amounts of (+)-diisopropyl tartrate followed by silylation furnished **1.50** in good yield and with high diastereoselectivity (*de* > 95%). Epoxide **1.50** was transformed into the primary amine **1.51** through a four step sequence involving protection-deprotection routines on the primary alcohol groups and a Staudinger reduction. The primary amine **1.51** smoothly underwent cyclization when heated in EtOH to afford **1.52**. This piperidine derivative is the product of a *6-endo-tet* cyclization in which S_N2-opening of the epoxide by nitrogen installs the correct stereochemistry of the future bridgehead

site (C8a). The corresponding *5-exo-tet* process is disfavored since it would lead to a *trans*-fused bicyclo[3.3.0]-nonane system.[82] Benzylation followed by desilylation and Swern oxidation furnished aldehyde **1.53**. A Sakurai reaction of aldehyde **1.53** with allyltrimethylsilane in the presence of titanium tetrachloride afforded the stereocenter at C(1). This gave alkene **1.54** in 71% yield with great diastereoselectivity (*de* > 95). The completion of the synthesis was attained through oxidative cleavage of **1.54** to provide aldehyde **1.55**, which upon reductive amination and global deprotection furnished (+)-castanospermine (**1.1**). In summary, Somfai and co-workers have attained **1.1** in an overall yield of 13% over 18 steps.

1.4.3 Mariano's Approach

In 1996 Mariano and co-workers[83] reported their first explorations of a pyridinium salt photoelectrocylization-aziridine ring-opening sequence. Later this methodology was combined with enzymatic hydrolysis using electric eel acetylcholinesterase (EEACE), thus affording efficient access to enantiopure cyclopentene building blocks like **1.56** (Scheme 1.10).[84-86] In 2005 Mariano[21] used this cyclopentene as starting point for a total synthesis of **1.1**. A central design feature in this approach was the ring rearrangement metathesis to form the piperidine ring of **1.1** followed by installation of the stereogenic centers at C(6) and C(7) by way of a regio- and diastereoselective hydroxylation process.



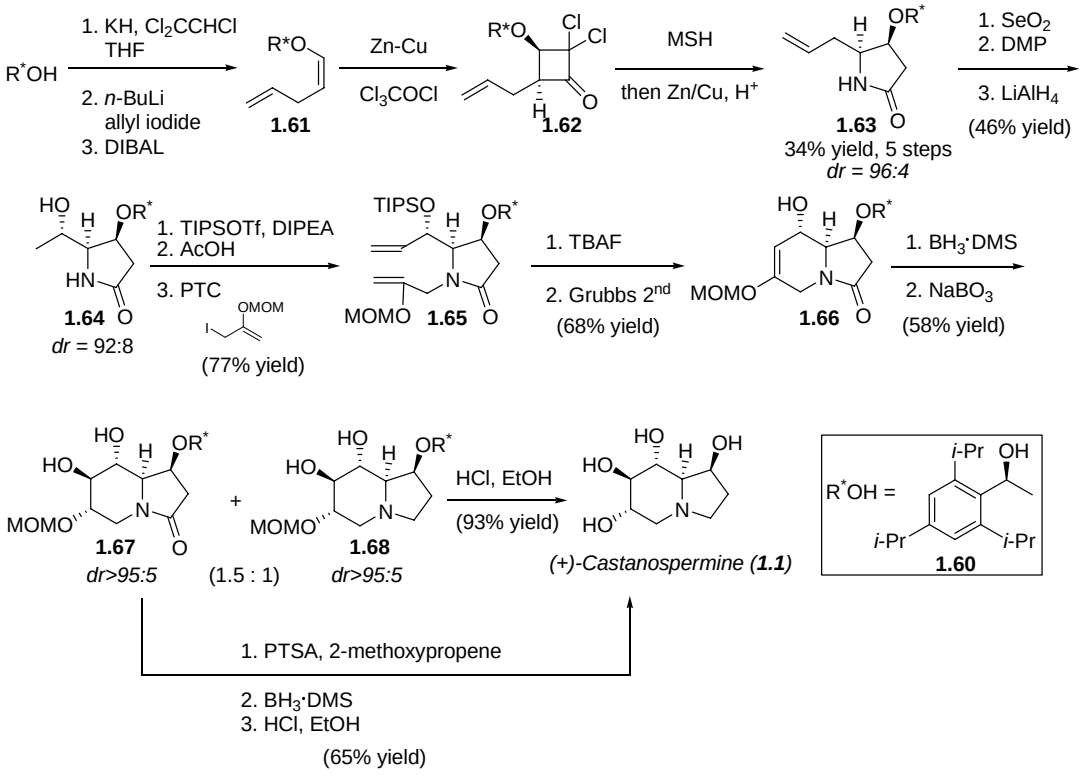
Scheme 1.10 Mariano's total synthesis of **1.1**.

Starting from **1.56**, a metathesis cascade using Grubbs 2nd generation catalyst **1.32** provided the tetrahydropyridine **1.57**. X-ray crystallographic analysis of tetrahydropyridine **1.57** revealed that it existed in a diaxial conformation. This preference probably stems from relief of $A^{1,3}$-strain between the *N*-acetyl and the allyl side chain in the alternative diequatorial conformation. Consequently, the hydroxy group at C(8) can be used to guide regio- and diastereoselective epoxidation of the

endocyclic alkene moiety. Vanadyl-mediated epoxidation of **1.57** produced epoxide **1.58**, a crucial intermediate in this concise synthesis of (+)-castanospermine (**1.1**). *trans*-Diaxial ring-opening under mild basic conditions followed by Brown hydroboration/oxidation provided the primary alcohol **1.59** in relatively poor yield for this four step sequence. Cyclization under Mitsunobu conditions followed by hydrogenolysis of the benzyl protection groups completed the synthesis of (+)-castanospermine (**1.1**). To summarize, Mariano have completed the total synthesis of **1.1** in 9 steps and 6.3% overall yield commencing from **1.56**.

1.4.4 Poisson's Approach

In 2006 Poisson and co-workers[87] revealed their first interest in a unified route to polyhydroxylated indolizidines completing the total synthesis of (−)-swainsonine and (+)-6-*epi*castanospermine. Later this strategy was implemented in the total synthesis of (+)-castanospermine (Scheme 1.11).[22] A central design feature was to deploy a diastereoselective [2 + 2] cycloaddition with dichloroketene in combination with a Beckmann ring expansion to forge the pyrrolidene moiety.



Scheme 1.11 Poisson's diastereoselective [2 + 2] cycloaddition approach to **1.1**.

The synthesis was initiated when the potassium alkoxide of (*R*)-stericol **1.60** was reacted with trichloroethylene. Subsequent treatment of this material with excess *n*-BuLi and allyl iodide afforded *cis*-*β*-elimination, chlorine-lithium exchange, and allylation of the ensuing lithio-ynol ether. This material was exposed to DIBAL providing *cis*-enolether **1.61**. Exposing **1.61** to *in situ* generated dichloroketene gave cyclobutanone **1.62** with excellent diastereoselectivity and subsequent Beckmann ring-expansion with Tamura's reagent (*O*-mesitylenesulfonyl-hydroxylamine, MSH) furnished the five-membered lactam **1.63**. Unfortunately, attempts to install the hydroxy group at C(8) in a diastereoselective manner using SeO_2 afforded a 1:1 diastereomeric mixture. This could, however, be remedied by subjecting this mixture to an oxidation/reduction sequence with DMP and $LiAlH_4$, which predominantly afforded the desired isomer **1.64** (*dr* = 92:8). Diene **1.65** was easily attained through bisilylation, selective hydrolysis of the silyl imidate, and *N*-allylation under phase-transfer conditions. Upon removal of the TIPS protecting group, the key RCM gave the bicyclic lactam **1.66** in good yield.

When **1.66** was exposed to hydroboration and oxidation, a 1.5:1 mixture of the bicyclic lactam **1.67** and the octahydroindolizidine **1.68** was obtained (both as single diastereomers *dr* > 95:5). All efforts to increase the amount of **1.68** relative to **1.67** were unrewarding, hence Poisson and co-workers decided to convert the bicyclic lactam **1.67** into the corresponding acetonide, which was readily reduced to a protected indolizidine and subsequently deprotected to furnish **1.1**. Moreover, octahydroindolizidine **1.68** was smoothly converted into **1.1** when treated with hydrochloric acid in ethanol. In summary, Poisson has realized the total synthesis of **1.1** in 16 steps and 1.8% overall yield starting from **1.60**. The highlights of this synthesis were a diastereoselective [2 + 2] cycloaddition followed by a Beckmann ring expansion to afford the five-membered moiety of (+)-castanospermine **1.60** and a metathesis-hydroboration/oxidation sequence to install the piperidine ring.

1.5 Summary

The natural product (+)-castanospermine (**1.1**) was first isolated and characterized in 1981. Recent biological studies have demonstrated that (+)-castanospermine may find use in the treatment of dengue virus and hepatitis C virus. Moreover, the highly condensed nature of (+)-castanospermine (**1.1**) continues to inspire synthetic chemists, and this has resulted in 11 syntheses since 1996.

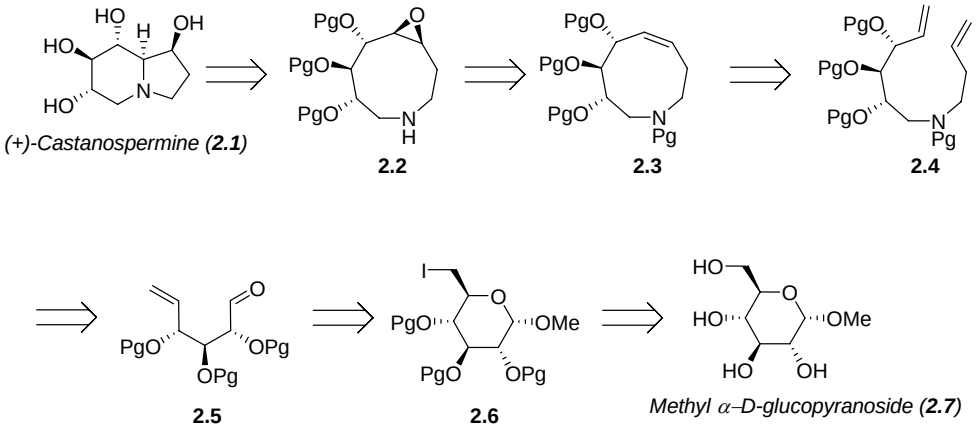
Unsurprisingly, the preferred chiral starting material is readily available D-glucose. The construction of the octahydroindolizidine skeleton has been achieved in several efficient ways, some of the most popular solutions involve RCM or reductive amination cascades. In 1999 Denmark disclosed the shortest synthesis of (+)-castanospermine reported to date. This synthesis clearly stands out, since it not only provides access to **1.1** in 8 steps from 2,5-dihydrofuran, but also serves as a general entry point to bicyclic azasugars.

2 The Total Synthesis of (+)-Castanospermine

2.1 Retrosynthetic Analysis and Synthetic Design

Our interest in (+)-castanospermine (**2.1**) arose from the acknowledgement of the important biological properties displayed by this natural compound and closely related congeners. Moreover, we sought to demonstrate the advantage of implementing two key metal-mediated protocols in a concise synthesis of (+)-castanospermine, which would provide the shortest synthesis of **2.1** starting from chiral pool material (cf. Chapter 1).

In designing our synthetic strategy toward (+)-castanospermine (**2.1**) the central feature was to construct the [5-6] indolizidine system of (+)-castanospermine through a strain-releasing transannular cyclization of expoxide **2.2** (Scheme 2.1). This epoxide could arise from diastereoselective epoxidation of the nine-membered cycloalkene **2.3**, which would in turn be accessed through a medium-ring metathesis reaction of an *N*-alkylated homoallyl amine of type **2.4**. Homoallyl amine **2.4** could originate from the unsaturated aldehyde **2.5** by suitable reductive amination conditions. The aldehyde **2.5** would be easily available from a protected derivative of methyl 6-iodoglucopyranoside **2.6** by a zinc-mediated reductive fragmentation.

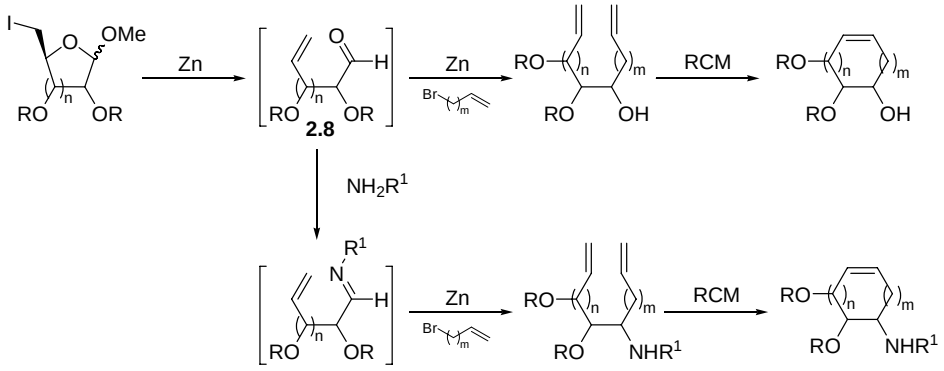


Scheme 2.1 Retrosynthesis of (+)-castanospermine.

Ultimately, the requisite iodopyranoside **2.6** would be attained from methyl α-D-glucopyranoside (**2.7**) through selective iodination of the 6-position followed by protection of the remaining hydroxy groups.

2.2 Background on the Zinc-Mediated Reductive Fragmentation

Carbohydrates are densely functionalized chiral molecules and thus serve as valuable starting materials for chemical synthesis. Since carbohydrates contain no C-C double bonds the primary obstacle in order to use these chiral building blocks in ring closing metathesis (RCM) is the efficient introduction of two olefins. This can be achieved in two separate steps using the zinc-mediated reductive fragmentation of ω-haloglycosides originally developed by Bernet and Vasella[88] to simultaneously provide a terminal alkene and liberate an aldehyde functionality at the anomeric center. The ensuing aldehyde can be transformed into an olefin utilizing a range of different organometallic reagents furnishing carbohydrate derived α,ω-dienes. In 1999 Madsen and co-workers[89,90] disclosed an elegant zinc-mediated tandem reaction converting ω-iodoglycosides into α,ω-dienes in one pot (Scheme 2.2). The zinc-mediated reductive fragmentation generated an aldehyde **2.8** that could be chain-elongated using *in situ* generated organozinc nucleophiles. Takai-methylenation[91,92] furnished the corresponding one carbon elongated product poised to undergo ring-closing metathesis. The methylenation reagent was formed *in situ* from diiodomethane and zinc in the presence of Lewis acid, typically TMSCl or $TiCl_4$, and a catalytic amount of $PbCl_2$.



Scheme 2.2 The zinc-mediated reductive fragmentation.

Moreover, the reductive fragmentation could be coupled with vinylation, which simultaneously afforded a two-carbon elongation and generated a novel stereocenter. The vinylation, however could not be performed under Barbier-type conditions, since zinc does not readily undergo oxidative addition to vinyl bromide. In the event, it was decided to preform divinyl zinc by magnesium-zinc transmetallation of vinylmagnesium bromide prior to the reaction. Arguable, the most powerful extension of this methodology was achieved when the reductive fragmentation was combined with zinc mediated Barbier-type allylation. This allowed for concomitant 3-carbon chain elongation and

generation of up to two stereocenters in one pot. Later developments revealed that the aldehyde moiety could be trapped with an amine providing an imine *in situ*, which in turn underwent zinc-mediated alkylation. Subsequent ring-closing metathesis efficiently provided access to amino sugar derivatives.[93]

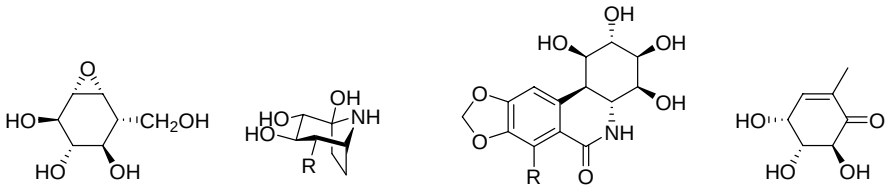
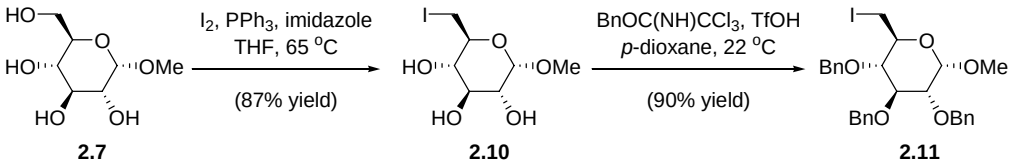


Figure 2.1 A selection of natural products prepared using the reductive fragmentation RCM methodology.

The methodology has played a critical role in the synthesis of several polyhydroxylated natural products by the Madsen laboratory including: conduritols,[90,94,95] (+)-cyclophellitol,[96] pancratistatin[97] and 7-deoxy pancratistatin,[98] gabosines, inositols,[99] and calystegines B_2, B_3, B_4, and A_3.[100-103] A selection of these molecules is depicted in Figure 2.1.

2.3 Synthesis of the Key Diene Intermediate[a]

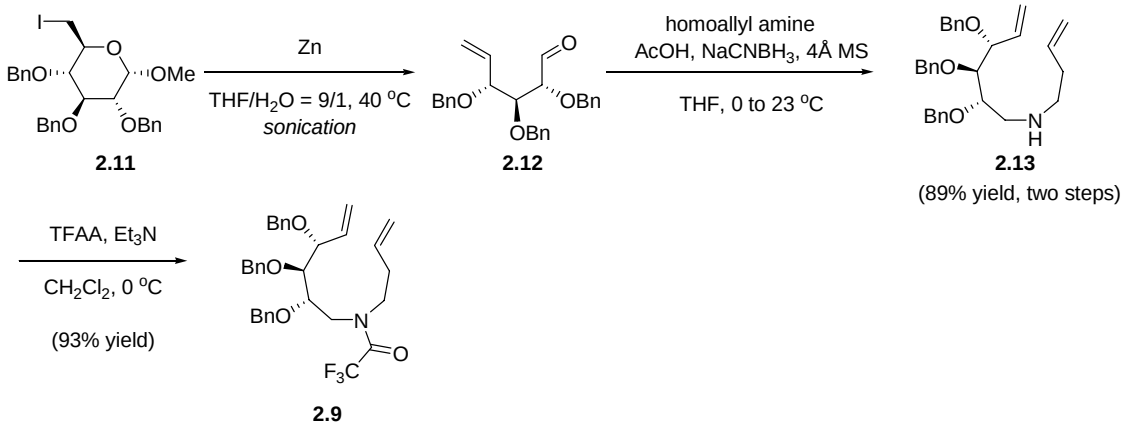
The construction of the prerequisite diene **2.9** became the first problem at hand. The synthesis commenced from cheap and commercially available methyl α-D-glucopyranoside (**2.7**). Initially this pyranoside was treated with iodine and triphenylphosphine in refluxing THF to give the desired selective iodination. The ensuing ω-iodopyranoside **2.10** was easily separated from triphenylphosphine oxide by use of reverse-phase column chromatography and isolated in 87% yield (Scheme 2.3). This product was conveniently recrystallized from ethanol in high yield.[104] Protection of the 2-, 3-, and 4-hydroxy groups as benzyl ethers was smoothly achieved by treating ω-iodopyranoside **2.10** with an excess of benzyl trichloroacetimidate under acidic conditions. This gave the desired benzyl-protected crystalline ω-iodopyranoside **2.11** in 90% yield.



Scheme 2.3 Preparation of ω-iodopyranoside **2.11**.

[a] Initial work on this project was conducted by Master student Mette Mikkelsen.

The attained tribenzyl ether **2.11** was sonicated in the presence of activated, powdered zinc to furnish unsaturated aldehyde **2.12**.[104] The aldehyde could easily be purified by use of silica-gel chromatography without epimerization of the α-stereocenter. However, upon standing this stereocenter epimerized readily, even when the compound was stored in the freezer, hence in practice the crude aldehyde was used directly in the subsequent step (Scheme 2.4).

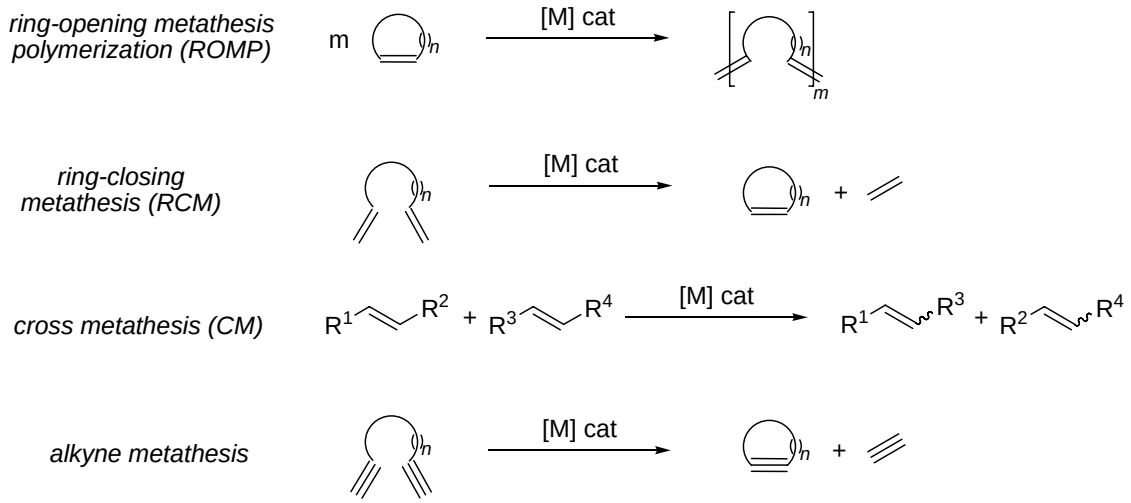


Scheme 2.4 Synthesis of the RCM precursor.

We attempted to perform the reductive amination as a one-pot sequence where **2.13** was formed in the presence of $NaCNBH_3$[105] or $NaBH(OAc)_3$,[106] homoallyl amine, and acetic acid. Unfortunately, these experiments provided the desired amine **2.13** in only a moderate yield along with reduced aldehyde and epimerized amine. Therefore it was decided to perform the zinc-mediated fragmentation and the reductive amination in two separate steps. After some experiments it was found that employing $NaCNBH_3$ as the reducing agent in the presence of an excess of homoallyl amine and powdered 4Å molecular sieves in THF furnished the desired amine in 89% yield. Careful adjustment to pH 7-8 using acetic acid and allowing for complete formation of the imine before adding $NaCNBH_3$ proved to be crucial in order to avoid epimerization and direct reduction of the aldehyde. The ensuing amine **2.13** was smoothly converted into the corresponding trifluoroacetamide **2.9** by treatment with trifluoroacetic anhydride in the presence of triethylamine, thus providing access to the requisite RCM precursor in only five steps from methyl α-D-glucopyranoside.

2.4 Background on the Ring-Closing Metathesis

The cyclization of diene precursors in the presence of transition metals with the simultaneous release of ethylene has advanced into one of the most useful reaction in modern organic synthesis. This process is known as the ring-closing olefin metathesis (RCM). The broadly accepted mechanism for the olefin metathesis known as the "carbene" mechanism was proposed by Hérisson and Chauvin in 1971[107] with key experimental evidence supporting this proposal being disclosed by the Grubbs,[108,109] Katz,[110-112] and Casey[113,114] groups. The mechanistic picture invokes metal carbene intermediates as propagating species in the catalytic cycle. These investigations prompted the development of well-defined catalysts from the Schrock group[115] at MIT and the Grubbs group[116] at Caltech. Following these pioneering investigations alkene metathesis has emerged into one of the most important C-C bond forming processes[a] in organic synthesis.[117-122] This was highly emphasized in 2005, the year the Nobel Prize was shared by R. H. Grubbs, R. R Schrock, and Y. Chauvin for their contributions to the development of highly efficient catalyst and advancement of the fundamental understanding of the mechanistic scenario of the olefin metathesis reaction.[123-125]



Scheme 2.5 A selection of metathesis reactions in organic synthesis.

Molybdenum and ruthenium catalysts have been applied to a broad repertoire of metathesis reaction (Scheme 2.5). Ring-opening metathesis polymerization (ROMP) has been put to great use in the preparation of macromolecules.[126,127] Recent advances in catalyst design, especially by Grubbs and

[a] The palladium catalyzed cross-coupling reactions are probably the only processes rivalling metathesis when considering the influence these reactions continue to have on the planning and execution of organic synthesis.

co-workers, have rendered cross-metathesis (CM) an important synthetic tool.[128,129] The youngest member of this family the ring-closing alkyne metathesis has primarily been utilized by the Fürstner group for macrocyclization.[130-133] In combination with partial hydrogenation under Lindlar conditions this methodology exclusively provides access to *Z*-isomers, thus providing an elegant solution to the lack of control over the configuration of the newly formed double bond in the traditional RCM when applied to macrocyclization.[134]

The most widely used metathesis catalyst are based on either molybdenum or ruthenium (Figure 2.2) Although complexes of metals such as tungsten,[135] rhenium,[136] and osmium[137] have found use in olefin metathesis, these exhibit lower stability and/or reactivity and have not attracted extensive investigations. The molybdenum catalyst **2.14** developed by Schrock[115] is one of the most active metathesis catalysts. This catalyst, however, is highly sensitive toward air and moisture, thus requiring a glove box for proper handling. Furthermore, only a limited range of polar functional groups are tolerated. In 1992 Grubbs and co-workers[57] disclosed the first well-defined ruthenium based metathesis catalyst **2.15** and three years later in 1995 complex **2.16** now known as Grubbs' 1st generation catalyst was published.[138] While the ruthenium based catalysts displayed lower reactivity than the molybdenum catalyst **2.14** this was outweighed by a higher stability toward air and moisture and greater functional group tolerance, assets making **2.16** one of the most widely used metathesis catalysts.

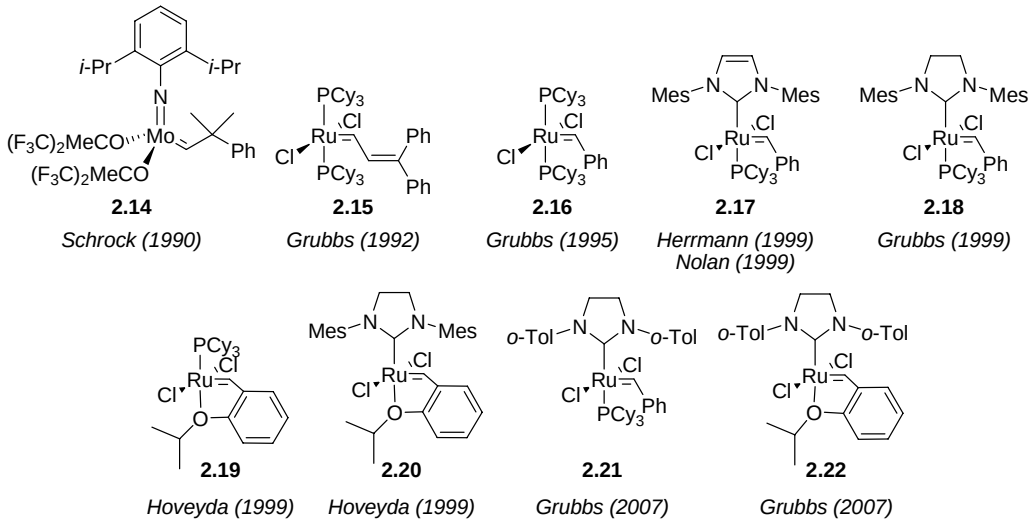
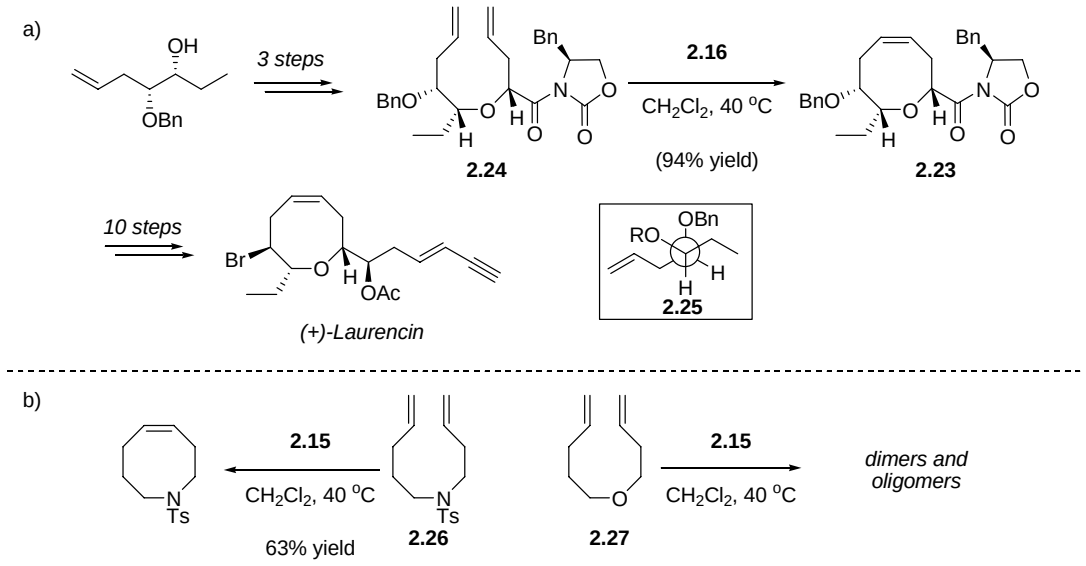


Figure 2.2 A selection of commonly used metathesis catalysts.

Following Arduengo's seminal report[139,140] on *N*-heterocyclic carbenes (NHC's) significantly more active catalysts **2.17** and **2.18** containing both phosphine and NHC ligands were disclosed almost simultaneously by Herrmann,[141] Nolan,[142] and Grubbs (2nd generation Grubbs' catalyst).[143] Along this line Hoveyda developed **2.19** and **2.20** bearing a chelating carbene ligand.[144,145] The family of Hoveyda catalysts, whose activity compares to the second generation Grubbs catalyst, is particularly useful for difficult metathesis cases of polysubstituted olefins. Two of the latest additions to this family of metathesis catalysts are **2.21** and **2.22**, which have been shown to offer great increases in activity for the formation of tetrasubstituted olefins via RCM and for the construction of disubstituted olefins containing allylic substituents.[129,146] This increased activity has been attributed to less steric hindrance around the ruthenium center.[147,148]

Ring-closing olefin metathesis has found widespread use in addressing the synthetic challenge of forming medium sized carbo- and heterocycles.[149-151] Medium sized rings are generally understood to contain 8 to 11 atoms within the ring.[152] The preparation of medium sized rings from acyclic precursors represents a significant challenge because of unfavorable enthalpic and entropic factors. The stereochemical features disfavoring medium sized ring formation are primarily bond angle deformations (Baeyer strain), forced adoption of eclipsed conformations (Pitzer strain), and most importantly transannular strain resulting from unfavorable interactions between groups that lie across the ring from one another. Moreover, there is a substantial entropic cost associated with the transition state leading to the cyclized product.[152] Therefore the formation of medium sized rings by RCM generally requires a diene that is conformationally predisposed to undergo cyclization or an appropriately placed functional group that can possible act as an internal ligand for the catalyst.[150] An example illustrating the use of appropriately placed substituents to facilitate ring closure was disclosed by Crimmins in 1999.[153,154] A crucial step in Crimmins and co-workers[154] total synthesis of (+)-laurencin was the RCM forming the eight-membered ether **2.23** (Scheme 2.6a).



Scheme 2.6 RCM for the formation of eight-membered rings.

In comparison Hoveyda[155] reported a successful RCM on sulfonamide linked diene **2.26** while the diene ether **2.27** exclusively produced dimers and oligomers when exposed to **2.15** (Scheme 2.6b). This significant difference was attributed to the vicinal stereocenters in **2.24**, which were suggested to induce a conformation positioning the olefinic chains close to each other by virtue of the *gauche* effect (cf. Newmann projection **2.25**). The contrast in efficiency of the depicted approaches to eight-membered rings clearly demonstrates that subtle structural differences can drastically influence, which reaction manifold is favored *i.e*. cyclization vs. dimerization and/or oligorimerization when RCM is applied to the formation of medium sized rings.

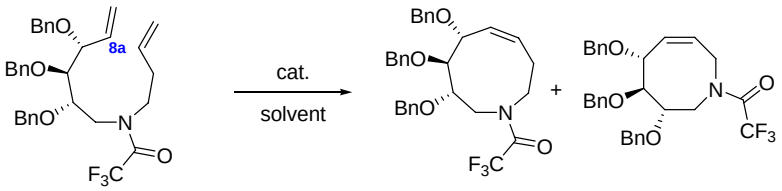
2.5 Completion of (+)-Castanospermine

2.5.1 Ring-Closing Metathesis Approach to the Azacyclononene

With access to gram quantities of diene **2.9** our focus shifted toward identifying suitable reaction conditions for the crucial ring-closing metathesis (Table 2.1). At the onset diene **2.9** was subjected to an array of metathesis catalysts **2.16**, **2.18**, **2.20**, **2.22**, **2.28**, and **2.29** under highly dilute conditions *i.e.* 0.2 mM in CH_2Cl_2 at 40 °C (entries 1-6). These reaction conditions afforded almost no conversion of the starting material, which could be recovered in nearly quantitative yield. Although discouraged by these initial results we found it reassuring that homodimeric cross-metathesis products were not observed under these conditions. Previously Percy and co-workers[156]

as well as Creighton and co-workers[157] have reported isolation of open-chain homodimers from RCM reaction run under high dilution. The low reactivity for the RCM can possibly be ascribed to the electron deficient nature of the olefin at C(8a) and the build-up of transannullar strain during cyclization *vide supra*. Moreover, it is conceivable that the sp^2-nature of the amide nitrogen enforces the pendant olefins to adopt an unproductive orientation, thus providing a significant barrier to cyclization.

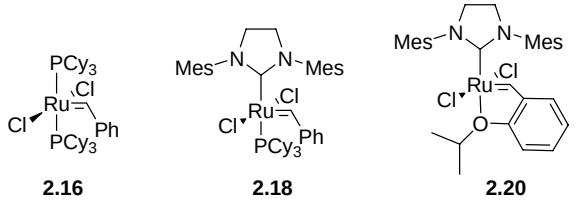
Table 2.1 Optimization of the RCM.



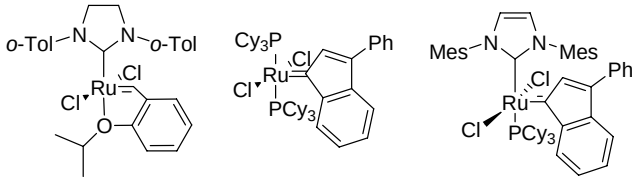
2.9 **2.30** **2.31**

entry	catalyst (20 mol%)	additive (30 mol%)	solvent	T(°C)	[M] (mM)	% yield (**2.30**)	% yield (**2.31**)
1	**2.16**	-	CH_2Cl_2	40	0.2	0	0
2	**2.18**	-	CH_2Cl_2	40	0.2	0	0
3	**2.20**	-	CH_2Cl_2	40	0.2	0	0
4	**2.22**	-	CH_2Cl_2	40	0.2	0	0
5	**2.28**	-	CH_2Cl_2	40	0.2	0	0
6	**2.29**	-	CH_2Cl_2	40	0.2	0	0
7	**2.16**	-	PhH	80	0.2	0	0
8	**2.18**	-	PhH	80	0.2	63	11
9	**2.20**	-	PhH	80	0.2	52	16
10	**2.22**	-	PhH	80	0.2	71	9
11	**2.28**	-	PhH	80	0.2	0	0
12	**2.29**	-	PhH	80	0.2	59	10
13	**2.22**	-	PhH	80	1.0	51	12
14	**2.22**[b]	-	PhH	80	0.5	78	7
15	**2.22**	$Ti(O\textit{i}\text{-}Pr)_4$	PhH	80	0.5	73	8
16	**2.22**	BHT	PhH	80	0.5	69	13
17	**2.22**[c]	-	PhH	80	0.5	52	5
18	**2.22**	-	PhMe	110	0.5	41	18

[a]Yield of isolated product. [b]Catalyst added over 20 h. [c]10 mol% catalyst added over 20 h



2.16 **2.18** **2.20**



2.22 **2.28** **2.29**

In order to circumvent these activation barriers we decided to perform the reaction in refluxing benzene. Significantly, neither Grubbs' 1st generation catalyst[138] **2.16** nor the Neolyst catalyst[158,159] **2.28** afforded conversion at these elevated temperatures (entries 7 and 11). We were especially surprised that the Neolyst catalyst failed to provide any of the desired cyclized product since this ruthenium indenylidene complex on several occasions has been reported to be particularly suitable for the formation of medium sized rings through RCM.[160,161] This effectiveness toward slow RCM reactions has been ascribed to higher stability in solution, however it remains unclear whether this originates from slow initiation, slow recapture of the catalytically active species or slow decomposition of the latter.[162] Gratifyingly, when the more reactive 2nd generation ruthenium carbene complexes where employed the desired nine-membered heterocycle **2.30** was attained in moderate to good yields (entries 8-9, and 12) A byproduct observed in all these reactions was the eight-membered *N*-heterocycle **2.31** which most likely stems from ruthenium-catalyzed isomerization of the electron rich terminal double bond prior to ring closure.[163-165] Several reports indicate that decomposition products of ruthenium-metathesis catalysts may be responsible for this type of side reaction.[166,167]

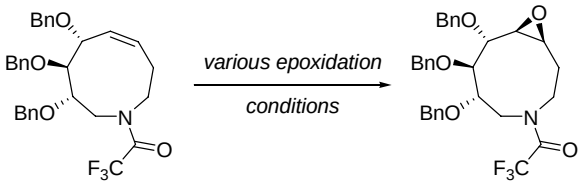
From the above experiments it was evident that the *N*-tolyl catalyst **2.22** recently developed by Grubbs, Schrodi and co-workers[146] was the catalyst of choice for this difficult metathesis reaction furnishing the desired heterocycle **2.30** in 71% yield along with only 9% of the undesired eight-membered heterocycle **2.31**. The superior performance of **2.22** in comparison to earlier versions of the NHC-type catalysts has previously been proposed to stem from the more open steric environment around the ruthenium center allowing the catalyst to accommodate more sterically demanding organic fragments.[129,148] Attempting to render this protocol amenable to scale-up we decided to perform the reaction at 1.0 mM concentration of diene **2.9** (entry 13). This unfortunately also provided considerable amounts of the homodimer. To our delight it was possible to obtain the prerequisite product **2.30** in 78% yield when the reaction was conducted at a 0.5 mM concentration adding the catalyst **2.22** slowly over 20 h (entry 14). Efforts to increase this yield even further by adding Ti(O*i*-Pr)$_4$ or BHT[168] did not prove fruitful (entries 15 and 16). The addition of Ti(O*i*-Pr)$_4$ is believed to break-up chelates formed between the ruthenium catalyst and substrate, which could potentially act unfavorably as catalyst sinks.[169-172] Moreover, decreasing the catalyst loading while maintaining the slow addition or increasing reaction temperature caused a decrease in yield (entries

17 and 18). Although a relatively high loading of **2.22** as well as highly dilute conditions were required to provide the desired nine-membered heterocycle **2.30** in good yield (entry 14) these optimized conditions did allow us to continue our synthetic explorations toward (+)-castanospermine (**2.1**).

2.5.2 The Transannular Cyclization

With the nine-membered heterocycle **2.30** in hand we sat out to investigate ways to perform the crucial diastereoselective epoxidation and transannular ring closure[5,160,173,174] that would ultimately provide the fused [5-6] indolizidine system of (+)-castanospermine. At the onset it was attempted to subject alkene **2.30** to standard Prilezhaev epoxidation conditions (Table 2.2).[175,176]

Table 2.2 Screening of epoxidation conditions.



2.30 **2.32**

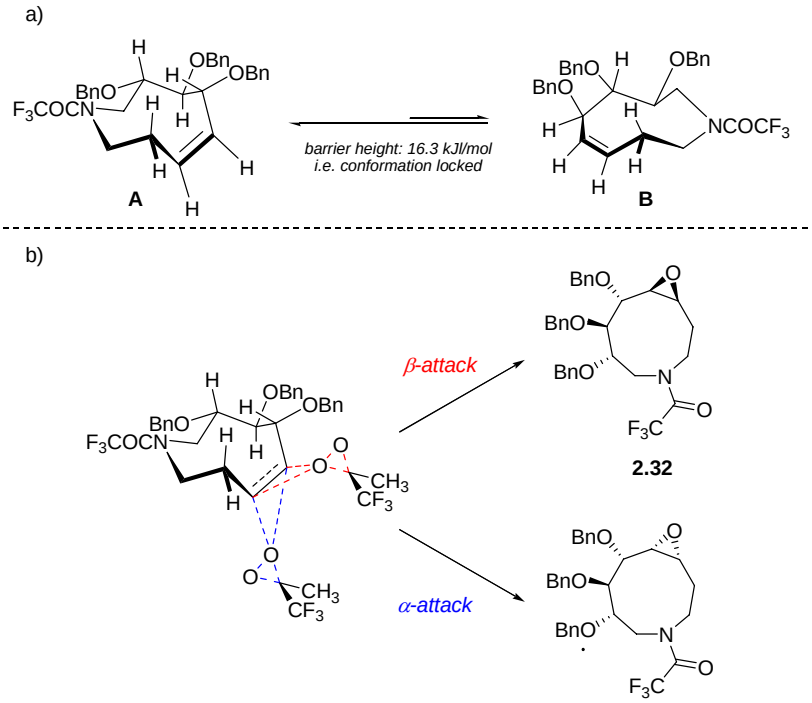
entry	oxidant	*catalyst*	additive	solvent	T(°C)	notes[a]
1	*m*CPBA	-	-	CH_2Cl_2	0	<10% conversion after 48 h
2	*m*CPBA	-	-	CH_2Cl_2	23	~80% conversion after 24 h one major product (~90%) and one minor
3	*m*CPBA	-	KF	CH_2Cl_2	23	<25% conversion after 48 h sluggish
4	*m*CPBA	-	Na_2HPO_4	CH_2Cl_2	23	<50% conversion after 48 h sluggish
5	*m*CPBA	-	$NaHCO_3$	CH_2Cl_2	23	<50% conversion after 48 h sluggish
6	oxone	-	CF_3COCH_3 $NaHCO_3$	CH_3CN	0	full conversion after 4 h one major product (~90%) and one minor product
7	DMDO	-	-	acetone	-15	full conversion after 6 h several products
8	UHP	-	TFAA Na_2CO_3	CH_2Cl_2	0	full conversion after 7 h several products
9	UHP	$MeReO_3$	-		23	full conversion after 48 h one major product (~90%) and one minor product

[a]Conversion and progress judged by TLC.

Treating **2.30** with *m*CPBA at 0 °C afforded less than 10% conversion after 48 h stirring while performing the same experiment at 23 °C led to almost full conversion into the requisite epoxide (entries 1 and 2). TLC analysis as well as ^{1}H NMR of the crude reaction mixture indicated the presence of two epoxides in >9:1 ratio.[a] Unfortunately all efforts to purify the desired epoxide **2.32**

[a] The absolute configuration of the major epoxide was deduced from the transannular cyclization product.

from this reaction mixture led to decomposition. Attempts to add KF to complex any *m*-chlorobenzoic acid present[177,178] or buffer[179] the reaction afforded slow conversion into the epoxide (entries 3 to 5). Luckily, it was found that the *in situ* generated dioxirane of 1,1,1-trifluoroacetone[180] cleanly converted **2.30** into the desired epoxide (^{1}H NMR revealed a >9:1 ratio of two epoxides, entry 6). A range of other epoxidation conditions[181,182] were also tested and only the $MeReO_3$-catalyzed epoxidation afforded considerable conversion into the desired epoxide (entries 7 to 9).



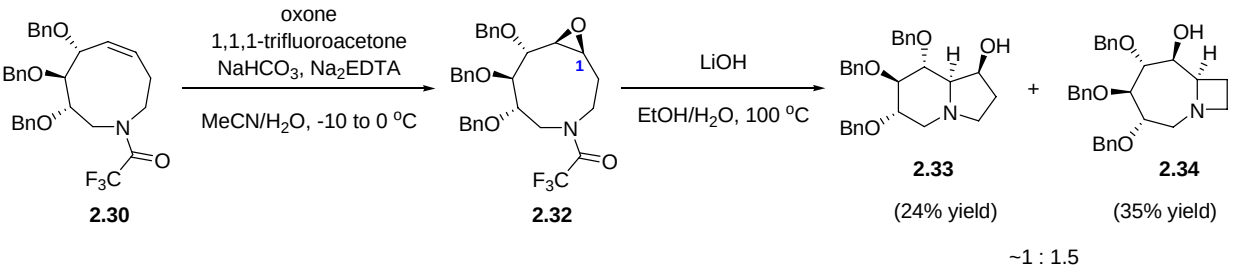
Scheme 2.7 Proposed transition state for the diastereoselective epoxidation.

A conformational search[183-186,a] on azacyclononene **2.30** revealed that this nine-membered ring is strongly biased toward conformation **A** which is 16.3 kJ/mol lower in energy than **B** (Scheme 2.7a). This conformational preference most likely stems from a minimization of transannular strain. Conformation **A** suggests that the *β*-face of the alkene is more open and therefore should be

[a] A conformational search using mixed torsional/low-mode sampling was carried out using Macromodel v. 9.6 release 110 as incorporated in the Maestro suite from Schrödinger Inc (for current versions, see http://www.schrodinger.com). The OPLS-2005 force field was used including the GB/SA salvation model with parameters suitable for water. Only structures within 21 kJ/mol of the global minimum were retained and the search was carried out for 50,000 steps to ensure completeness. The author acknowledges assistant Professor Peter Fristrup for valuable assistance in conducting the conformational search.

preferentially attacked by an external oxidant, thus providing a reasonable explanation for the observed diastereoselectvity (Scheme 2.7b).[187-189]

Having identified suitable reaction conditions for the diastereoselective epoxidation our focus shifted toward the key transannular cyclization. The crude epoxide was used directly for this step to avoid decomposition of the labile epoxide during work-up. Inspired by conditions developed by White and Hrnciar[190] we treated the crude epoxide **2.32** with an excess of LiOH in a mixture of EtOH/H_2O at 100 °C. TLC revealed multiple products, however, the desired and known octahydroindolizidine **2.33** was isolated in 24% yield (Scheme 2.8).[5] Structural analysis of the byproducts revealed the strained bicyclic compound **2.34** as a major component isolated in 35% yield. While the formation of **2.34** was unexpected due to its highly strained nature the generation of **2.34** may most likely be ascribed to the close proximity of the amine moiety to C(1).[a]

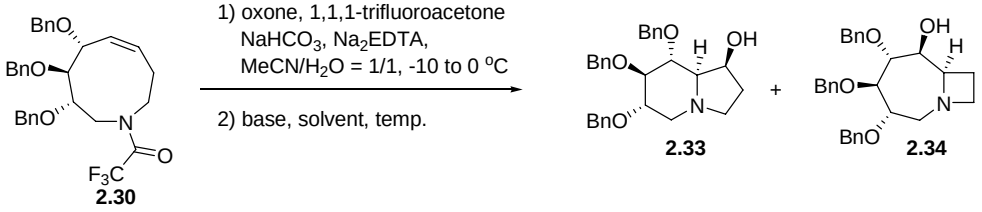


Scheme 2.8 Initial attempt to perform the transannular cyclization.

In efforts to maximize the formation of the desired octahydroindolizidine **2.33** a range of different deprotection/cyclization conditions were surveyed and the ratio between **2.33** and **2.34** was judged by ^{1}H NMR of the crude reaction mixture (Table 2.3). Using LiOH to facilitate the deprotection and subsequent cyclization in different solvent mixtures at 50 °C did improve this ratio slightly (entries 1-3). When the reaction was conducted at lower temperatures using KO(*t*-Bu) in combination with one equivalent of water to mediate the deprotection, **2.33** was attained as the major product in a 4:1 ratio (entries 4, 7 and 8).[191] The counterion proved to be of importance since neither NaO(*t*-Bu) nor LiO(*t*-Bu) afforded full conversion of the starting material.

[a] The structure of this byproduct has been assigned by extensive 2D NMR-studies.

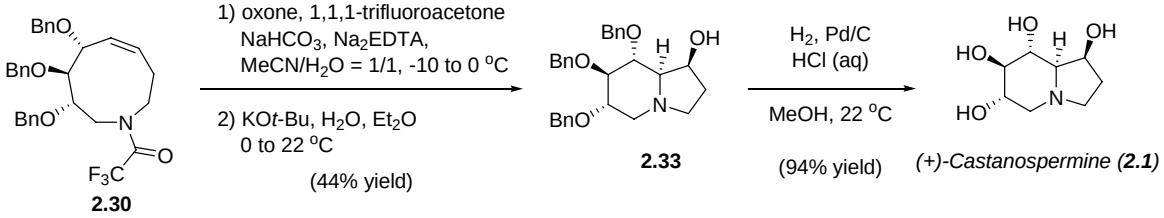
Table 2.3 Optimization of the transannular cyclization.



entry	base	additive	solvent	T(°C)	**2.33** : **2.34**[a]
1	LiOH	-	EtOH/H_2O=1:1	100	1:1.5
2	LiOH	-	EtOH/H_2O=1:1	50	1:1.2
3	LiOH	-	THF/MeOH/H_2O=2:2:1	50	1:1
4	KO(*t*-Bu)	H_2O	Et_2O	23	2.3:1
5	NaO(*t*-Bu)[b]	H_2O	Et_2O	23	1.9:1
6	LiO(*t*-Bu)[b]	H_2O	Et_2O	23	1.4:1
7	KO(*t*-Bu)	H_2O	Et_2O	0	4:1
8	KO(*t*-Bu)	H_2O	Et_2O	-78	3.7:1

[a] Ratio determined by ^{1}H NMR. [b] Less than 50% conversion as judged by ^{1}H NMR.

Gratifyingly, when azacyclononene **2.30** was subjected to our optimized epoxidation/cyclization sequence the desired octahydroindolizidine **2.33** was obtained in 44% overall yield for these three chemical transformations *i.e.* diastereoselective epoxidation, deprotection, and concomitant transannular closure (Scheme 2.9).

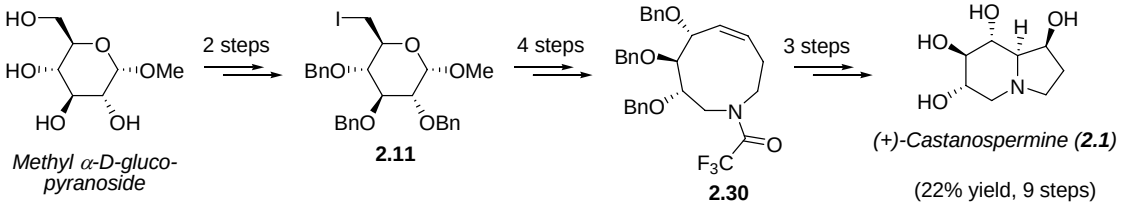


Scheme 2.9 Completion of (+)-castanospermine (**2.1**).

When **2.33** was exposed to deprotection conditions reported by Miller and Chamberlin[5] we obtained (+)-castanospermine (**2.1**) in 94% yield with all spectral data in accordance with literature data.

2.6 Summary

We have successfully prepared (+)-castanospermine (**2.1**) in a highly concise manner. The synthesis comprises no more than nine steps from methyl α-D-glucopyranoside and provides the natural product in 22% overall yield (Scheme 2.10). Only the asymmetric synthesis reported by Denmark in 1999 provides a more concise route to (+)-castanospermine (**2.1**).



Scheme 2.10 Key intermediates in the total synthesis of (+)-castanospermine (**2.1**).

The key steps in our synthetic approach are a zinc-mediated reductive fragmentation of **2.11**, a challenging ruthenium-catalyzed ring-closing metathesis affording **2.30**, and a strain-driven *N*-deprotection/transannular cyclization cascade. Moreover, this synthesis underscores the effectiveness of employing a zinc-fragmentation ring-closing metathesis sequence in the development of highly efficient synthetic routes from carbohydrates.

2.7 Experimental

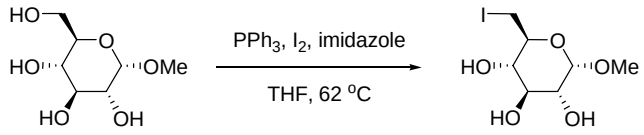
2.7.1 Materials and Methods

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AC-200 MHz or a Varian Mercury 300 MHz. Chemical shifts were measured in ppm and coupling constants in Hertz (Hz). The shifts were measured relative to the signals for residual $CHCl_3$ (7.26 ppm), $CDCl_3$ (77.0 ppm), CD_3OD (4.84 ppm), and CD_3OD (49.05 ppm). Multiplicities are reported as follows; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet. All ^{13}C NMR spectra were proton decoupled. IR spectra were obtained by use of a Bruker-α-P FT-IR spectrophotometer or a Perkin-Elmer 1600 FTIR spetrophotometer using either thin films or a KBr matrix (for solids) and are reported in wavenumbers (cm^{-1}). Melting points were obtained from a H. Heidolph and Schwabach, type 10 apparatus and are uncorrected. Thin layer chromatography was performed on aluminium plates precoated with silica gel (Merck; 60 F_{254}) using the solvent systems indicated. Compounds were visualized by illumination using a UV lamp (254 nm) or by charring after dipping in a solution of anisaldehyde (15 g) in ethanol (250 mL) and concentrated sulfuric acid (2.5 mL). Chromatographic purifications were performed by silica-gel chromatography[192,193] using Amicron Matrex 60 Å; 35-70 μm. Optical rotations were measured on a Perkin Elmer 241 polarimeter operating on the sodium D line with a path length of 100 mm and are reported as: $[\alpha]^{T}$ (concentration in g/100mL, solvent). All compounds on which HRMS were performed

exhibited pure ^{1}H NMR spectra and showed one spot by TLC analysis. HRMS analyses were conducted by Dr. Kenneth B. Jensen, the Mass Spectrometry Laboratory, Department of Chemistry, University of Southern Denmark, Odense or by Dr. Gustav Bojesen the Mass Spectrometric Research Unit, Department of Chemistry, University of Copenhagen. Commercially available reagents were used as received unless otherwise indicated. Air- and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of argon from a manifold or balloon. All solvents were of HPLC grade. Tetrahydrofuran, diethyl ether, and toluene were distilled under nitrogen from Na-benzophenone prior to use. Dichloromethane was dried over 4 Å molecular sieves. Dimethylsulfoxide was distilled under a positive pressure of argon and stored over 4 Å molecular sieves.

2.7.2 Synthesis of (+)-Castanospermine

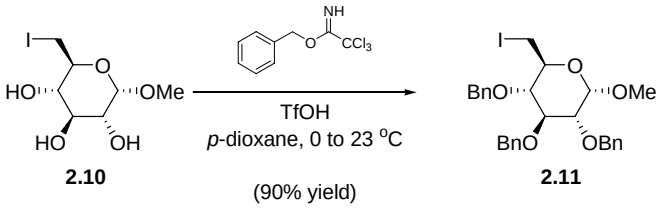
Methyl 6-deoxy-6-iodo-D-glucopyranoside (2.10)



Methyl α-D-glucopyranoside — **2.10**

A solution of methyl α-D-glucopyranoside (4.5 g, 23.2 mmol), Ph_3P (9.13 g, 34.8 mmol), and imidazole (3.16 g, 46.4 mmol) in THF (180 mL) was heated to reflux. I_2 (8.83 g, 34.8 mmol) was dissolved in THF (50 mL) and added to the reaction mixture in a dropwise manner. The resulting yellow/orange solution was refluxed until TLC revealed full conversion of the starting material (typically 2 h). The mixture was allowed to cool to room temperature, filtered, and concentrated *in vacuo* to afford a yellow/orange syrup. The syrup was purified by reverse phase column chromatography (H_2O:MeOH = 9:1) to afford **2.10** (6.14 g, 87% yield) as a white solid: mp = 146-148 °C (EtOH), lit.[104] mp = 147-148 °C (EtOH); R_f = 0.22 ($CHCl_3$:MeOH = 9:1); ^{1}H NMR (300 MHz, D_2O) δ 4.86 (d, *J* = 3.6 Hz, 1H), 3.80-3.68 (m, 2H), 3.66 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.53 (s, 3H), 3.52-3.46 (m, 2H), 3.4 (q, *J* = 8.8 Hz, 1H); ^{13}C NMR (75.4 MHz, D_2O) δ 100.0, 74.1, 73.1, 71.8, 70.8, 56.0, 7.2; IR (Neat) 3434, 3289, 2978, 2912, 2867, 2843, 1456, 1409, 1373, 1240, 1142, 1062, 1032, 1011, 991, 884, 749 cm^{-1}. Spectral data are in accordance with literature values.[104]

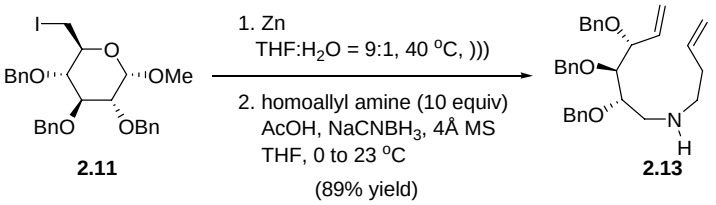
Methyl 2,3,4-tris-*O*-benzyl-6-deoxy-6-iodo-D-glucopyranoside (2.11)



2.10 **2.11**

Iodosugar **2.10** (1.0 g, 3.30 mmol) was placed in a 100 mL round bottom flask, dissolved in 1,4-dioxane (22.0 mL), and benzyltrichloroacetimidate (3.74 g, 14.8 mmol) was added. The pale yellow solution was cooled to 0 °C by use of an ice/water bath. Triflic acid (500 μL) was added in a dropwise manner until pH < 1, the cooling was removed and the resulting dark orange solution was stirred at 23 °C for 50 min. The reaction mixture was diluted with diethyl ether (50 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL). The phases were separated and the organic phase was washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a viscous oil. The crude oil was purified by flash chromatography (98:2 → 95:5 → 90:10, Heptane-EtOAc, dry-loaded using SiO_2) to afford **2.11** (1.57 g, 90% yield) as a viscous colorless oil that crystallized upon standing; mp = 60-61 °C, lit.[104] mp = 61-62 °C (heptane-EtOAc); R_f = 0.18 (heptane:EtOAc = 7:3); $[\alpha]_D^{21}$ = +33.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 15H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 4.81 (d, *J* = 11.4 Hz, 2H), 4.69 (d, *J* = 10.9 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 3.58 Hz, 1H), 4.02 (dd, *J* = 9.5, 8.8 Hz, 1H), 3.54 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.50-3.43 (m, 2H), 3.42 (s, 3H), 3.37-3.27 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.5, 138.0, 137.9, 128.5, 128.5 (two peaks), 128.4, 128.1, 128.0, 128.0, 127.9, 127.7, 98.1, 81.5, 81.4, 80.0, 75.8, 73.4, 69.2, 55.5, 7.7; IR (Neat) 3089, 3065, 3030, 3003, 3986, 2897, 2865, 1497, 1454, 1359, 1194, 1138, 1088, 1029, 736 cm^{-1}. Spectral data are in accordance with literature values.[104]

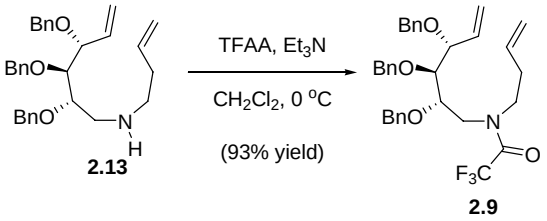
But-3-enyl-((2*S*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-hex-5-enyl)-amine (2.13)



2.11 (2.0 g, 3.75 mmol) was placed in a 100 mL conical flask and dissolved in a mixture of THF (16.9 mL) and water (1.88 mL). Zn (2.46 g, 37.6 mmol) was added and the flask was immersed into a sonication apparatus preheated to 40 °C. The solution was sonicated for 1 h upon which TLC revealed full conversion of the starting material. The suspension was filtered through a plug of celite using Et_2O (50 mL). Saturated aqueous $NaHCO_3$ (25 mL) was added to the filtrate, the phases were separated, and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale yellow viscous oil. The crude oil was purified by flash chromatography (9:1 $\rightarrow$ 4:1; heptane:EtOAc) to afford aldehyde **2.12** as a colorless oil (1.55 g, 99%). The oil was used directly in the next step since the aldehyde epimerizes when stored in the freezer. 4Å powdered molecular sieves (7.43 g, 2.0 g/mmol) was placed in 100 mL round bottom flask and activated by use of heat gun (5 min heating under high vacuum 1-2 mbar). The aldehyde (1.55 g, 3.71 mmol) and homoallyl amine (2.64 g, 37.1 mmol) were dissolved in THF (65.6 mL) and added to the round bottom flask. AcOH (2.75 mL) was added in a dropwise manner until pH = 7-8. The suspension was cooled to 0 °C by use of an ice/water bath. After 30 min stirring was $NaCNBH_3$ (1.17 g, 18.6 mmol) added in one portion and the mixture was allowed to warm to 21 °C. The reaction mixture was stirred for 14 h and then quenched by addition of saturated aqueous $NaHCO_3$ (25 mL). The mixture was filtered and the filter cake was washed with EtOAc (3 x 50 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a pale yellow oil. The crude product was purified using flash chromatography (CH_2Cl_2:MeOH = 9:1) to afford **2.13** (1.56 g 89% over two steps) as a colorless oil; R_f = 0.23 (CH_2Cl_2:MeOH = 9:1); $[\alpha]_D^{21}$ = -39.4° (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 15H), 5.86 (ddd, *J* = 14.0, 9.9, 7.6 Hz, 1H), 5.62 (ddt, *J* = 13.8, 10.3, 7.0 Hz, 1H), 5.31-5.19 (m, 2H), 4.98 (ddd, *J* = 13.8, 3.0, 1.5 Hz, 1H), 4.95-4.91 (m, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.00 (dd, *J* = 7.5, 4.7 Hz, 1H), 3.79

(dd, *J* = 11.4, 5.7 Hz, 1H), 3.55 (t, *J* = 5.0 Hz, 1H), 2.69 (dd, *J* = 12.4, 5.0 Hz, 1H), 2.59 (dd, *J* = 12.4, 6.8 Hz, 1H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.06 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.4, 138.1, 136.0, 135.5, 128.2, 128.1, 127.8, 127.5, 118.5, 116.2, 82.0, 80.3, 78.6, 74.7, 73.1, 70.4, 49.4, 48.7, 33.8; IR (Neat) 3088, 3065, 3029, 2976, 2863, 1496, 1454, 1392, 1351, 1330, 1306, 1207, 1088, 1067, 996, 917, 734, 697 cm^{-1}; HRMS (ESI+) calc'd for $C_{31}H_{37}NO_3Na$ ($[M+Na]^+$) 494.2666, found 492.2647.

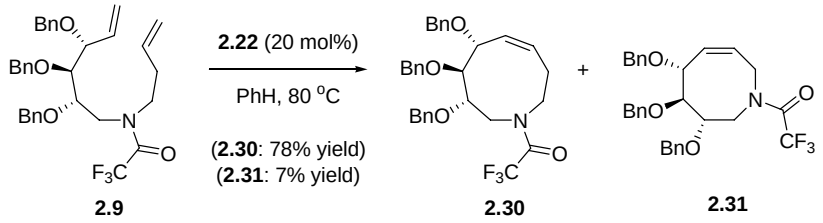
But-3-enyl-((2*S*,3*S*,4*R*)-2,3,4-tris-benzyloxy-hex-5-enyl)-trifluoroacetamide (2.9)



Amine **2.13** (1.13 g, 2.30 mmol) was dissolved in dichloromethane (24.0 mL), Et_3N (1.0 mL, 727 mg, 7.2 mmol) was added and the solution was cooled to 0 °C by use of an ice/water bath. Trifluoroaceticanhydride (680 μL, 1.0 g, 4.8 mmol) was added in a dropwise manner and the reaction mixture was stirred for 30 min at 0 °C. The mixture was diluted with dichloromethane (50 mL) and quenched with saturated aqueous $NaHCO_3$ (25 mL) at 0 °C. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (98:2 → 95:5, heptane-EtOAc) to afford **2.9** (1.26 g, 93% yield) as a viscous colorless oil; R_f = 0.41 (heptane:EtOAc = 70:30); $[\alpha]_D^{21}$ = -52.8 (*c* 2.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) **major rotamer**: δ 7.34-7.14 (m, 15H), 5.90 (ddd, *J* = 17.3, 10.4, 7.9 Hz, 1H), 5.72-5.46 (m, 1H), 5.32 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.29-5.21 (m, 1H), 5.06-4.91 (m, 2H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.15 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.06 (ddd, *J* = 8.6, 5.0, 3.4 Hz, 1H), 3.77 (dd, *J* = 13.9, 3.4 Hz, 1H), 3.52-3.29 (m, 4H), 2.19 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ **major rotamer**: 157.1 (q, J_{CF} = 35.6 Hz), 138.1, 138.1, 138.0, 135.1, 133.3, 128.4, 128.4, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.6, 119.3, 117.8, 116.4 (q, J_{CF} = 288 Hz), 80.7, 80.2, 76.0, 73.9. 73.8, 70.6, 48.8, 48.6, 32.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ **major rotamer**: -69.43 (s, 3F); **minor rotamer**: -68.34 (s, 3F); IR (Neat) 3089, 3067, 3032, 2910,

2871, 1687, 1454, 1252, 1206, 1144, 1122, 1089, 1072, 735, 698 cm^{-1}; HRMS (ESI+) calc'd for $C_{33}H_{36}F_3NO_4Na$ ($[M+Na]^+$) 590.2489, found 590.2472.

(3*S*,4*S*,5*R*)-3,4,5-tribenzyloxy-1-trifluoroacetyl-1-aza-cyclonon-6-en (2.30) and (3*S*,4*S*,5*R*)-3,4,5-tribenzyloxy-1-trifluoroacetyl-1-aza-cyclooct-6-en (2.31)

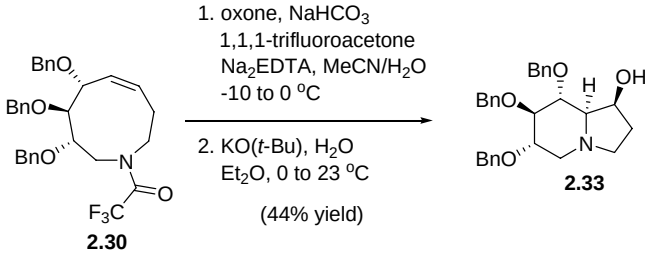


Diene **2.9** (100 mg, 0.185 mmol) was dissolved in benzene (370 ml, 0.5 mM). The solution was degassed using sonication (5 min under a positive flow of Ar). The solution was heated to 80 °C. The catalyst **2.22** (21 mg, 0.037 mmol) was dissolved in benzene (20 mL) and added to the reaction mixture in a dropwise manner over 20 h by use of a syringe pump. After 24 h stirring the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford a dark green oil. The crude oil was purified using flash chromatography (98:2 → 95:5, heptane-EtOAc) to afford **2.30** (78 mg, 78%) as a colorless oil that crystallized upon standing and **2.31** (6.8 mg, 7%) as a colorless oil.

2.30: mp = 76-77 °C (heptane-EtOAc); R_f = 0.18 (heptane:EtOAc 9:1); $[\alpha]_D^{21}$ = +33.8 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ **major rotamer**: 7.46-7.13 (m, 15H), 5.93-5.84 (m, 1H), 5.72 (t, *J* = 10.0 Hz, 1H), 4.87 (d, *J* = 11.1 Hz, 1H), 4.83 (d, *J* = 10.7 Hz, 1H), 4.70 (t, *J* = 11.3 Hz, 2H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.38-4.27 (m, 1H), 4.05 (ddd, *J* = 9.3, 6.7, 2.9 Hz, 1H), 3.93 (dd, *J* = 14.0, 2.7 Hz, 1H), 3.90-3.81 (m, 1H), 3.66 (dd, *J* = 8.4, 6.7 Hz, 1H), 3.41 (dd, *J* = 13.9, 9.1 Hz, 1H), 3.07-2.76 (m, 1H), 2.55-2.11 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ **major rotamer**:158.7 (q, J_{CF} = 35.4 Hz), 138.6, 138.5, 138.1, 133.7, 129.0, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 118.1, 116.2 (q, J_{CF} = 288 Hz), 114.3, 84.5, 78.1, 75.0, 74.6, 73.3, 70.6, 51.9, 48.5, 27.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ **major rotamer**: -69.6 (s, 3F); **minor rotamer**: -67.9 (s, 3F); IR (Neat) 3090, 3062, 3031, 2929, 2900, 2871, 1692, 1454, 1205, 1144, 1093, 1068, 736, 698 cm^{-1}; HRMS (ESI+) calc'd for $C_{31}H_{32}F_3NO_4Na$ ($[M+Na]^+$) 562.2176, found 562.2152.

2.31: R_f = 0.20 (heptane:EtOAc 9:1); 1H NMR (300 MHz, $CDCl_3$) δ **major rotamer**: 7.39-7.19 (m, 15H), 5.89-5.58 (m, 2H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 2H), 4.59 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.37 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.13 (dd, *J* = 8.5, 5.6 Hz, 1H), 4.02 (d, *J* = 13.8 Hz, 1H), 3.82-3.65 (m, 4H); 13C NMR (50.3 MHz, $CDCl_3$) δ **major rotamer**: 157.0 (q, J_{CF} = 37.0 Hz), 138.3, 138.2, 137.8, 134.2, 128.3, 127.9, 127.7, 126.0, 116.4 (q, J_{CF} = 287 Hz), 83.5, 78.5, 77.3, 74.6, 72.8, 71.8, 47.2, 46.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ **major rotamer**: -69.5 (s, 3F); **minor rotamer**: -68.2 (s, 3F); IR (Neat) 3088, 3063, 3031, 2924, 2870, 1692, 1497, 1454, 1206, 1184, 1143, 1100, 1028, 736, 697 cm^{-1}; $[\alpha]_D^{22}$ = +23.9 (c 0.85, $CHCl_3$); HRMS (ESI+) calc'd for $C_{30}H_{30}NO_4Na$ ($[M+Na]^+$) 548.2020 , found 548.2036.

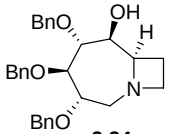
(1*S*,6*S*,7*R*,8*R*,8a*R*)-1-Hydroxy-6,7,8-tribenzyloxy-indolizidine (2.33).



Oxone (114 mg, 0.185 mmol) and $NaHCO_3$ (24 mg, 0.286 mmol) were added to a solution of Na_2EDTA (186 µL, 0.4 mM in H_2O), 1,1,1-trifluoroacetone (100 µL), and CH_3CN (500 µL) precooled to -10 °C by use of a MeOH/ice bath. Within 5 min stirring the suspension became pale yellow. **2.30** (20 mg, 0.037 mmol) was dissolved in CH_3CN (500 µL) and added in a dropwise manner. The mixture was allowed to warm to 0 °C and stirred for 4 h upon which TLC revealed full consumption of **2.30**. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 x 2.5 mL) and the combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude oil was dissolved in Et_2O (7.4 mL) and the solution was cooled to 0 °C. H_2O (1.2 µL, 0.064 mmol) and KO(*t*-Bu) (71 mg, 0.634 mmol) were added. After 30 min stirring the mixture was allowed to warm to room temperature and stirred for an additional 10 h. H_2O (2.5 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 2.5 mL). The combined organics were dried over K_2CO_3, filtered, and concentrated under reduced pressure. The crude oil was purified by preparative TLC (heptane:CH_2Cl_2:MeOH 7:7:2) to afford **2.33** (7.6 mg, 44% over two steps) as a pale yellow oil: R_f = 0.42 (7:7:2, heptane:CH_2Cl_2:MeOH); $[\alpha]_D^{21}$ = +35.5

(*c* 0.96, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.22 (m, 15H), 4.99 (d, *J* = 10.9 Hz, 1H), 4.87 (d, *J* = 11.6 Hz, 2H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.31-4.14 (m, 1H), 3.74-3.62 (m, 2H), 3.61-3.51 (m, 1H), 3.26 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.16-3.00 (m, 1H), 2.26-2.06 (m, 1H), 2.00 (t, *J* = 10.4, 1H), 1.94 (dd, *J* = 9.4, 3.6 Hz, 1H), 1.79-1.71 (m, 1H), 1.40 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.8 (2C), 138.4, 128.5 (3C), 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 87.3, 79.2, 76.9, 75.6, 74.3, 72.9, 71.8, 70.7, 54.3, 51.6, 33.6; IR (Neat) 3450, 3088, 3063, 3030, 2925, 2855, 2812, 1713, 1678, 1606, 1497, 1454, 1400, 1167, 1135, 1097, 1068, 1028, 734, 697 cm^{-1}; HRMS (ESI+) calc'd for $C_{29}H_{33}NO_4Na$ ($[M+Na]^+$) 482.2303, found 482.2293. Spectral data are in accordance with literature values.[5]

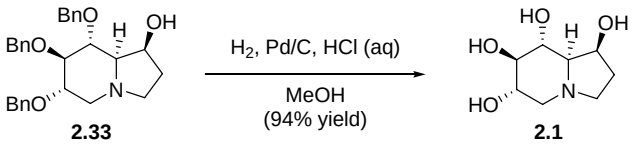
(3*S*,4*R*,5*R*,6*S*,7*R*)-3,4,5-Tris-benzyloxy-1-aza-bicyclo[5.2.0]nonan-6-ol (2.34)



2.34

2.34 was isolated as a byproduct from the strain-releasing cyclization of **2.32** as a pale yellow oil: R_f = 0.23 (heptane:CH_2Cl_2:MeOH = 7:7:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 15H); 4.82 (d, *J* = 10.9 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.71 (d, *J* = 6.3 Hz, 1H), 3.76 (dd, *J* = 7.0, 2.7 Hz, 1H), 3.70-3.57 (m, 3H), 3.44 (t, *J* = 7.6 Hz, 1H), 3.30-3.19 (m, 1H), 3.09 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.04-2.93 (m, 3H), 2.46 (dd, *J* = 10.7, 8.9 Hz, 1H), 2.33-2.18 (m, 1H), 1.90-1.81 (m, 1H); IR (Neat) 3420, 3030, 2923, 2852, 1497, 1363, 1261, 1211, 1139, 1095, 734, 697 cm^{-1}; HRMS (ESI+) calc'd for $C_{29}H_{33}NO_4Na$ ($[M+Na]^+$) 482.2303, found 482.2281.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrahydroxy-indolizidine, (+)-Castanospermine (2.1)



2.33 (23.7 mg, 0.0516 mmol) was dissolved in MeOH (7.1 mL). Pd/C (23 mg, 10% Pd) and concentrated HCl (78 μL) were added. The mixture was stirred under an H_2-atmosphere at room temperature for 48 h upon which TLC revealed full conversion of **2.33**. Amberlite (1.0 g, Amberlite IRA-400(OH)) was added. After 2 h stirring the solution was filtered through a plug of celite

utilizing MeOH. The filtrate was concentrated under reduced pressure to provide (+)-castanospermine (**2.1**) (9.2 mg, 94%) as colorless oil that crystallized slowly. An analytical sample was prepared by recrystallization from EtOH: mp 209-213 ^{o}C dec (lit. mp 212-215 ^{o}C); ^{1}H NMR (300 MHz, D_2O) δ 4.43-4.25 (m, 1H), 3.65-3.59 (m, 1H), 3.60 (t, *J* = 9.3 Hz, 1H), 3.32 (t, *J* = 9.1 Hz, 1H), 3.18 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.08 (dt, *J* = 9.2, 2.1 Hz, 1H), 2.39-2.29 (m, 1H), 2.21 (q, *J* = 9.2 Hz, 1H), 2.06 (t, *J* = 10.7 Hz, 1H), 2.02 (dd, *J* = 9.8, 4.5 Hz, 1H), 1.71 (dddd, *J* = 13.8, 8.7, 8.5, 1.3 Hz, 1H); ^{13}C NMR (50.3 MHz, D_2O) δ 78.0, 70.4, 69.1, 68.6, 68.0, 54.4, 50.6, 31.7; IR (Neat); $[\alpha]_D^{21}$ = +72.4° (c 0.22, H_2O); HRMS (ESI+) calc'd for $C_8H_{15}NO_4Na$ ($[M+Na]^+$) 212.0894, found 212.0888. In accordance with literature data.[1]

3 Synthesis of the Macrocyclic Core of (–)-Pladienolide B

3.1 Natural Product Inspired Drug Discovery

Natural products have played a major role in the development of organic chemistry on both a theoretical and experimental level. The diverse natural product landscape has proven itself to be an invaluable resource in the search for lead agents of medicinal importance.[194] The impact of biologically active natural products on drug development manifests itself in virtually every major therapeutic area. Nearly 50% of the drugs approved since 1994 are based on natural products.[195] Currently over a 100 natural-product-derived compounds are undergoing clinical trials and more than 100 similar projects are in preclinical trials.[196]

One concern associated with natural products in relation to drug development is that these compounds were not designed for human therapeutics. Hence, while many of these molecules exhibit excellent *in vitro* and *in vivo* activities they may not be suitable as drugs due to undesirable pharmacokinetic properties and undesired side effects.[197] Analogs can be pursued by *post* manipulation of the natural product, however, this practice is often complicated by the functional groups already in place. Another bottleneck in the development of interesting leads from natural products is their often limited availability from natural sources.[198] This supply issue can in some cases *e.g.* the anticancer agent (+)-discodermolide[199-203] be resolved through total synthesis. Nonetheless some natural products are too complex to manufacture a practical fashion, which will impact supply. Diverted total synthesis (DTS) or function oriented synthesis (FOS) are two similar concepts recently coined by Danishefsky[204] and Wender,[198] respectively. The central principle of these two concepts is that the function of a biologically active natural product can be imitated, fine-tuned or improved by replacement with simpler molecular scaffolds designed to incorporate the pharmacophoric elements of the lead natural product. The identification of simpler scaffolds will allow for shorter synthesis thereby circumventing the supply issue and for facile lead optimization.[198,204]

An interesting example illustrating this concept are Wender's studies and syntheses of bryostatin analogs.[205] The bryostatins are highly complex natural products isolated from marine bryozoa in only 0.00014% yield (Figure 3.1).[206] This family of natural products has attracted much attention as

anticancer agents due to their ability to induce apoptosis in cancer cells.[207] Furthermore, studies have revealed that bryostatins enhance learning and memory in animal models, which suggests a potential use in the treatment of cognitive impairments.[208]

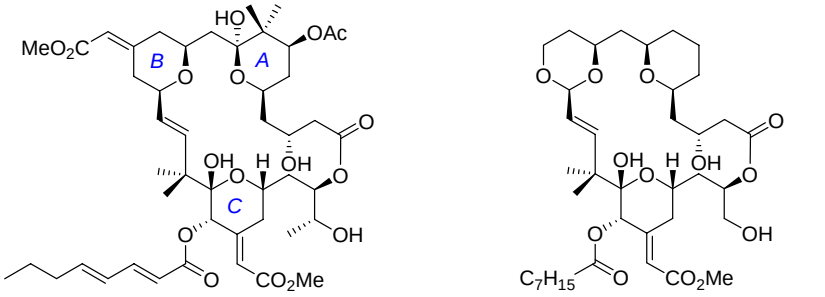


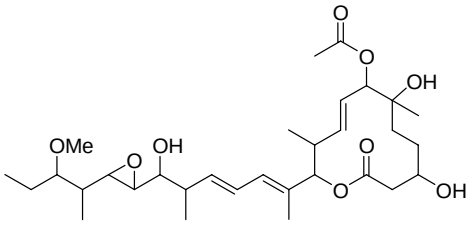
Figure 3.1 Bryostatin 1 (**3.1**) and lead analog **3.2**.

Until Trost'[209] recent and very concise synthesis of bryostatin 16 (39 total steps, 26-step longest linear sequence) chemical syntheses[210-212] of bryostatins required > 70 total steps. Based on pharmocophoric modeling and extensive synthetic studies Wender and co-workers[205,213] realized the preparation of the bryostatin analog **3.2** with protein kinase C (PKC) affinities comparable to naturally occurring bryostatin 1 (**3.1**). Importantly, **3.2** was available in 29 total steps, a savings of 10 steps over the shortest synthesis of bryostatin. This illustrates how the design of new simplified analogs can lead to molecules superior in function to the natural product and which are accessible in fewer steps.

3.2 The FD-895 and Pladienolide Polyketides

3.2.1 Isolation and Structural Determination

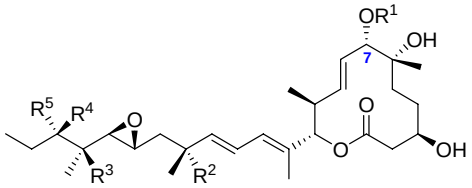
FD-895 (**3.3**, Figure 3.2) and the pladienolides (Figure 3.3) belong to a structurally unique family of 12-membered macrocyclic polyketides. FD-895 (**3.3**) was isolated in 1994 by Mizoue and co-workers[214] from the fermentation broth of *Streptomyces hygrosopicus*. In 2004 the pladienolides were isolated from *Streptomyces platensis* Mer-11107 by way of an assay targeting compounds that inhibit cell signaling pathways in a tumor-specific microenvironment (Figure 3.3).[215-217] These novel polyketides contain a 12-membered macrocyclic core, a 12-carbon diene side-chain, up to 11 stereocenters and an *E*-olefin embedded in the macrocyclic ring.



FD-895 (**3.3**)

Figure 3.2 Planar structure of macrolide FD-895 (**3.3**).

While the absolute configuration of FD-895 (**3.3**) still remain elusive the absolute configurations of pladienolide B (**3.5**) and pladienolide D (**3.7**) were recently determined by NMR and synthetic studies.[168,218] The stereochemistry of the other congeners are hitherto unknown, but are expected to follow from **3.5** and **3.7**.



compound	R^1	R^2	R^3	R^4	R^5
pladienolide A (**3.4**)	H	H	H	H	OH
pladienolide B (**3.5**)	Ac	H	H	H	OH
pladienolide C (**3.6**)	Ac	H	H	=O	
pladienolide D (**3.7**)	Ac	OH	H	H	OH
pladienolide E (**3.8**)	Ac	H	OH	H	OH
pladienolide F (**3.9**)	H	OH	H	H	OH
pladienolide G (**3.10**)	H	H	OH	H	OH

The stereochemical assignment of pladienolide B (**3.5**) and pladienolide D (**3.7**) were recently determined by NMR and synthetic methods. Stereochemistry of the congerners are expected to follow from **3.5** and **3.7**, but have yet to be confirmed.

Figure 3.3 Structure of pladienolides (A-G).

3.2.2 Biological Activity

FD-895 (**3.3**) exhibited potent *in vitro* anticancer activity against numerous cultured tumor cells with IC_{50}-values ranging from 2-8.0 ng/mL. Moreover, FD-895 (**3.3**) showed strong cytocidal activity against HL-60/ADR cells, which are resistant to the DNA intercalating anticancer drug adriamycin.[214] Six of the seven pladienolides were reported to inhibit hypoxia-induced gene expression of vascular endothelial growth factor (VEGF) in U251 human glioma cells (Table 3.1).[215] The most active pladienolides *i.e.* B, C and D had IC_{50}-values in the low nanomolar range (entries 2-

4). Furthermore the pladienolides inhibited cancer cell growth.[215] Interestingly, pladienolides B, C, and D all have the C(7) acetyl group (pladienolide numbering) in place (cf. Figure 3.3). Lack of this acetate decreased the biological activity by more than two orders of magnitude as witnessed by pladienolides A, F, and G (entries 1 and 6,7).[215]

Table 3.1 Inhibition of hypoxia-induced VEGF-PLAP secretion and anti-proliferative activity of pladienolides.

entry	compound	anti-VEGF-PLAP activity IC_{50} (nM)	anti-proliferative activity IC_{50} (nM)
1	pladienolide A (**3.4**)	451.5	967.5
2	pladienolide B (**3.5**)	1.8	3.5
3	pladienolide C (**3.6**)	7.4	14.7
4	pladienolide D (**3.7**)	5.1	6.0
5	pladienolide E (**3.8**)	65.2	146.8
6	pladienolide F (**3.9**)	2894.2	2595.2
7	pladienolide G (**3.10**)	> 10,000	> 10,000

In addition pladienolide B (**3.5**) was tested in a 39-cell cancer panel experiment, which indicated that the compound has a unique mode of antitumor action unlike those of anticancer drugs currently in clinical use.[217] Notably, pladienolides B (**3.5**) and D (**3.7**) also caused *in vivo* tumor regression in several human cancer xenograft models. In the most sensitive model, using BSY-1 human breast tumor xenografts in nude mice, tumors were completely regressed at day 15 after the first administration of pladienolide B(**3.5**).[217] It has recently been reported that a derivative of pladienolide B has entered human clinical trials for cancer.[219]

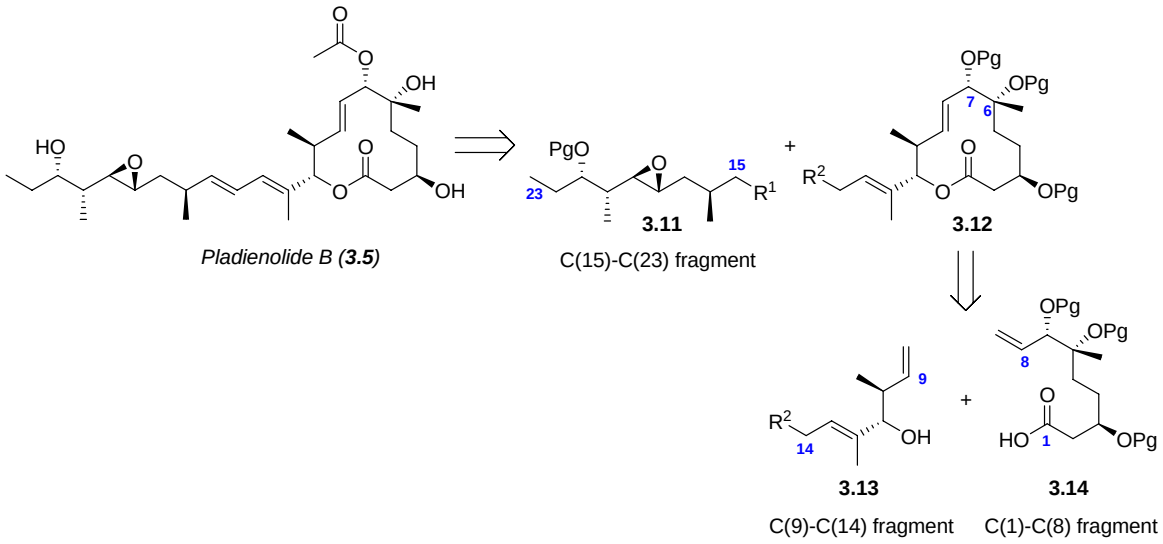
In 2007 Kotake and co-workers[220] from Eisai, Co., Ltd. in Japan utilized differently tagged pladienolide B (**3.5**) and D (**3.7**) derivatives as chemical probes to identify their target protein and elucidate their mode of action. These studies led to a proposed mechanism involving binding to the splicing factor SF3b an essential component of the spliceosome.[220] The spliceosome is an intracellular complex consisting of multiple proteins and ribonucleoproteins. This molecular assembly is the main cellular machinery guiding RNA-splicing, that is, the removal of non-coding introns from precursor messenger RNA (pre-mRNA).[221,222] It has been suggested that splicing events may play an essential role in cancer development, thus inhibition of the spliceosome could serve as a novel target for anticancer drugs.[223-227]

3.3 Previous Synthetic Efforts Toward the Pladienolide Family of Natural Products

The unique biological profile of pladienolide B has spurred considerable interest from the scientific community. Kotake and co-workers[168] disclosed the first total synthesis of pladienolide B in 2007, whereas Burkart and co-workers[228] have conducted synthetic studies on the pladienolide B side-chain. The subsequent discussion will be limited to Kotake's total synthesis.

3.3.1 Kotake's Total Synthesis of Pladienolide B

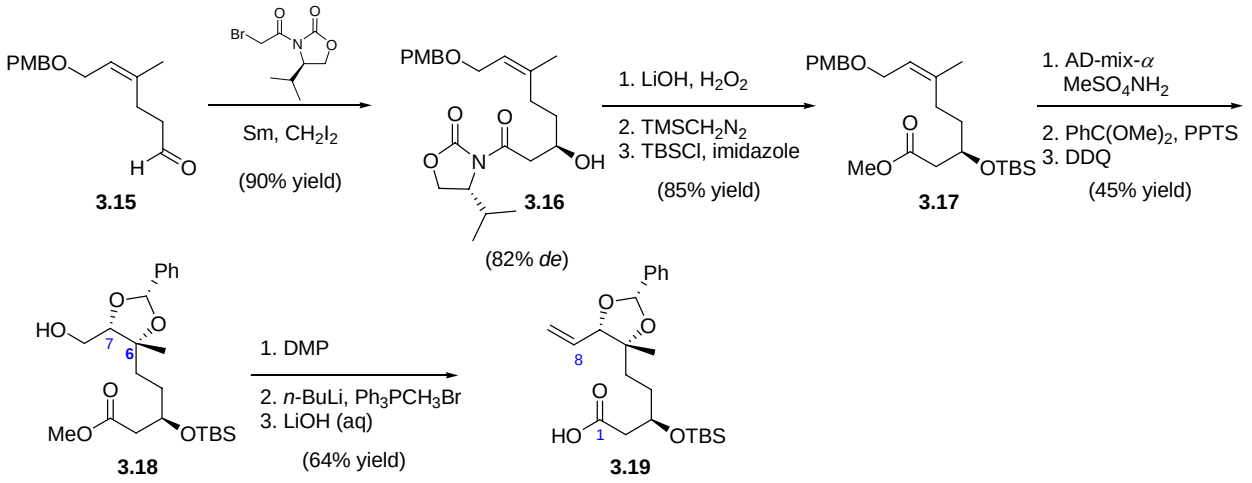
The central design feature in Kotake's approach to pladienolide B (**3.5**) was to install the stereogenic centers in a reagent-controlled manner (Scheme 3.1). Additionally, it was planned to build **3.5** through the coupling of the side-chain moiety **3.11** and the macrolide core **3.12**. The macrolide core **3.12** was build from **3.13** and **3.14** employing an esterification and RCM sequence.[168]



Scheme 3.1 Kotake's convergent approach to pladienolide B (**3.5**).

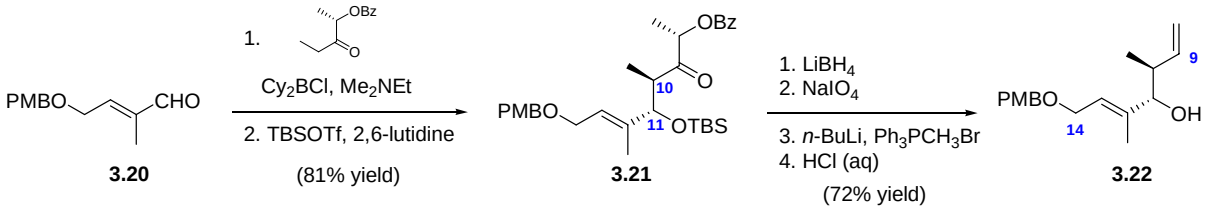
Kotake's synthesis of the C(1)-C(8) fragment **3.14** commenced from aldehyde **3.15** which is available in two steps from nerol (Scheme 3.2).[229] When **3.15** was subjected to the Sm(II)-mediated asymmetric Reformatsky reaction disclosed by Fukuzawa and co-workers[230] β-hydroxy amide **3.16** was attained in 90% yield and 82% *de*. β-hydroxyamide **3.16** was smoothly converted into methyl ester **3.17** through a three step sequence. In order to install the hydroxy groups at C(6) and C(7) Kotake[168] employed the Sharpless asymmetric dihydroxylation. Unfortunately, the asymmetric dihydroxylation only proceeded in 76% *de* and the resulting diastereomers were inseparable.

Benzylidene acetal protection of this mixture followed by removal of the PMB-group and recrystallization furnished the primary alcohol **3.18** as a single diastereomer. Sequential oxidation, Wittig olefination, and methyl ester hydrolysis gave the requisite C(1)-C(8) fragment **3.19**.



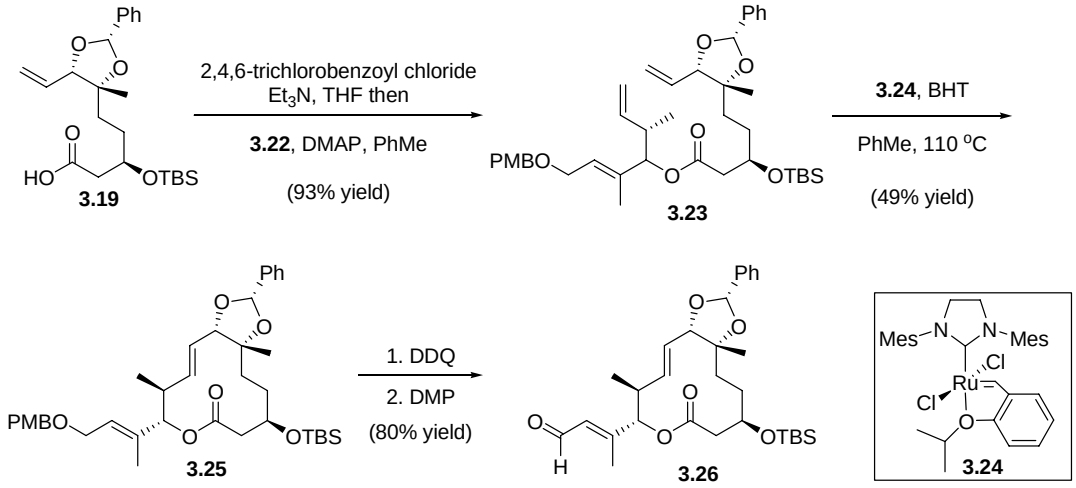
Scheme 3.2 Kotake's synthesis of the C(1)-C(8) fragment **3.19**.

Construction of the C(9)-C(14) fragment **3.22** began with installation of the C(10) and C(11) stereogenic centers employing an *anti*-aldol reaction developed by Paterson and co-workers (Scheme 3.3).[231] Aldehyde **3.20** was exposed to the boron-enolate generated from a chiral ketone and Cy_2BCl, affording **3.21** upon silylation. An additional four steps including oxidative cleavage and Wittig methylenation furnished the prerequisite C(9)-C(14) unit **3.22**.[168]



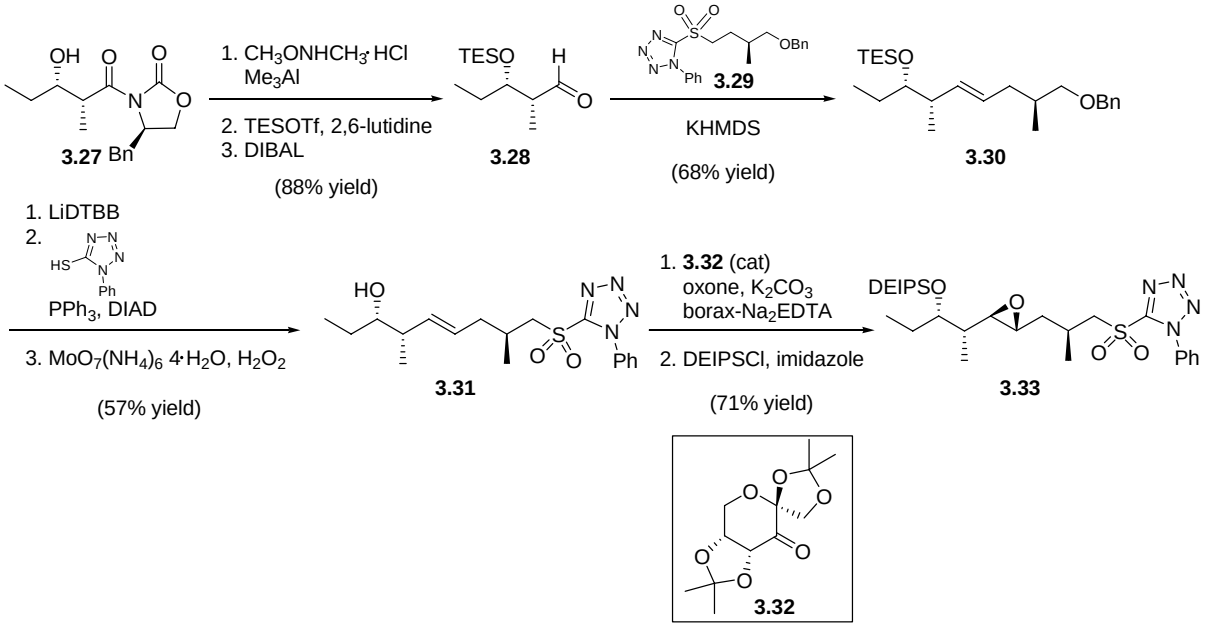
Scheme 3.3 Kotake's synthesis of the C(9)-C(14) fragment **3.22**.

The C(1)-C(8) fragment **3.19** and the C(9)-C(14) fragment **3.22** were unified by means of a Yamaguchi-type[232] esterification reaction (Scheme 3.4). Acid **3.19** was treated with 2,4,6-trichlorobenzoyl chloride and the ensuing mixed acid anhydride was subjected to alcohol **3.22** and DMAP furnishing triene **3.23** in excellent yield. The central 12-membered lactone **3.25** was formed in moderate yield through a demanding RCM.[168] Subsequent deprotection and oxidation gave **3.26**, poised to undergo coupling with a side-chain fragment.



Scheme 3.4 RCM approach to macrolide moiety **3.26**.

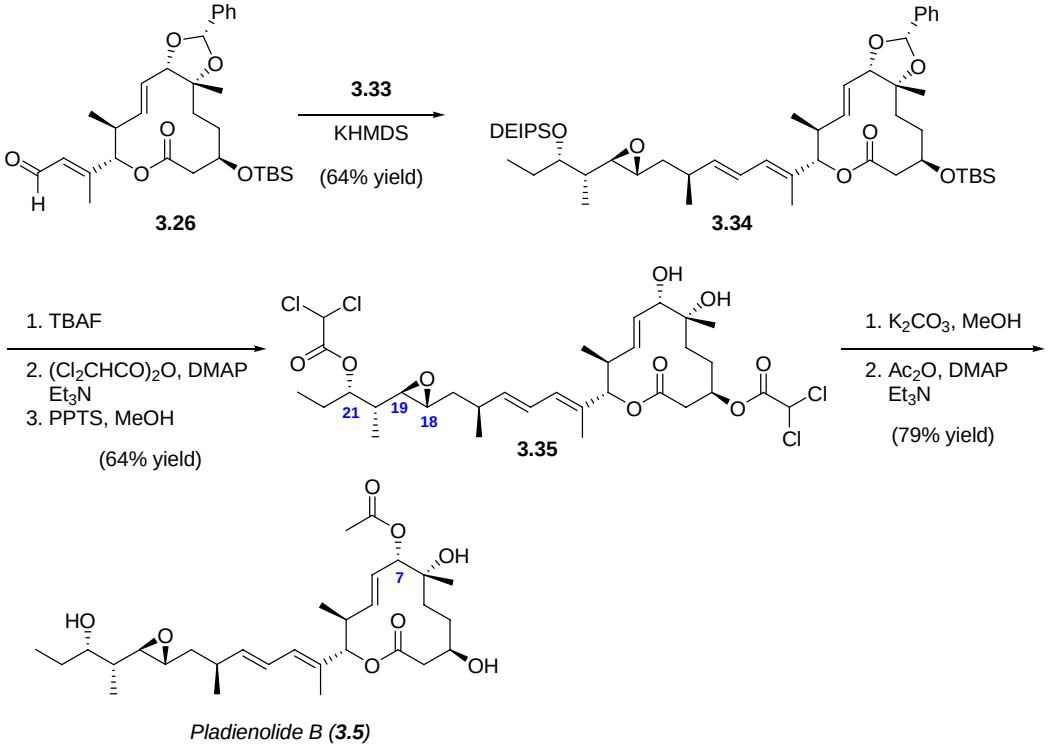
Preparation of the side-chain C(15)-C(23) fragment **3.33** started from the known *β*-hydroxy amide **3.27** (Scheme 3.5).[168] Treating **3.27** with *N*,*O*-dimethylhydroxylamine hydrochloride and trimethyl aluminium furnished the corresponding Weinreb amide, which upon silylation and DIBAL-reduction gave aldehyde **3.28** in excellent yield for this three step sequence. Next, the Julia-Kocienski-olefination[233] was employed to couple **3.29** and aldehyde **3.28**, which provided the requisite *trans*-olefin **3.30** exclusively.



Scheme 3.5 Synthesis of the C(15)-C(23) side-chain fragment **3.33**.

After removal of the benzyl-group, the ensuing alcohol was transformed into sulfone **3.31** with concomitant desilylation during the oxidation. The side-chain fragment was completed utilizing the asymmetric Shi-epoxidation[234,235] followed by silylation to afford the desired epoxide **3.33** as a single diastereomer after recrystallization.

With access to the side-chain fragment **3.33** and macrolide **3.26** Kosake and co-workers[168] sought to couple these employing the Julia-Kocienski-olefination (Scheme 3.6). In the event, exposing macrolide **3.26** to sulfone **3.33** and KHMDS afforded the desired *E*,*E*-diene **3.34** in good yield. Initial attempts to effect global deprotection of **3.34** under acidic conditions were hampered by the hydrolytic stability of the benzylidene group as well as opening of the epoxide by the C(21) hydroxy group forming a tetrahydrofuran ring. Therefore, the two silyl-groups were converted into acid-stable dichloroacetyl groups and the benzylidene group was removed with PPTS and MeOH furnishing diol **3.35**. Ultimately, methanolysis of **3.35** followed by regioselective acetylation of the more nucleophilic hydroxy group at C(7) gave pladienolide B **3.5**.



Scheme 3.6 Kotake's end-game.

In summary, Kotake and co-workers[168] have completed the first total synthesis of pladienolide B. The longest linear sequence contains 22 steps from nerol providing **3.5** in 2.1% overall yield. This synthesis confirmed the absolute stereochemistry of pladienolide B (**3.5**). Key to the completion of **3.5** was the implementation of a RCM reaction to forge the 12-membered macrolide. Additionally, the exploitation of the Julia-Kocienski-olefination to install the side-chain allows for late-stage modifications and provides a practical route to novel pladienolide B analogs.

3.4 Idea, Stereochemical Rationale, and Retrosynthesis

Our interest in pladienolide B and closely related congeners was prompted by the highly interesting biological profile displayed by this family of natural products. The highly potent *in vitro* and *in vivo* antitumor activity as well as the unique mechanism of action presented by this class of compounds makes pladienolide B (**3.5**) a promising lead structure in the identification of novel anti-cancer agents. At the onset of our synthetic endeavors in April 2005 only the planar structure of pladienolide B had been reported.[216] Structurally, the macrocyclic core of pladienolide bares a strong resemblance to 10-deoxymethynolide (**3.36**) the aglycon of the known antibiotic neomethymycin that is produced by *Streptomyces venzuelae* (Figure 3.4).[236] Moreover the side-chain of pladienolide B is closely related to the side-chain of herboxidiene (**3.37**), which was isolated from *Streptomyces A7947*.[237,238] From an evolutionary point of view it is feasible that pladienolide B (**3.5**) and other secondary metabolites such as 10-deoxymethynolide (**3.36**) and herboxidiene (**3.37**) could be synthesized by polyketide synthases encoded by related gene clusters.[239-242] Consistent with a common biogenesis for these polyketides we hypothesized that the absolute stereochemistry of the macrocyclic core **3.38** would correlate with that of **3.36** and **3.37**. Thus we focused our synthetic studies on the projected core structure **3.38**, the enantiomer of the (+)-pladienolide B (**3.5**) core. A successful synthesis of this macrocyclic core could potentially clarify whether it is the core structure that is responsible for the biological activity. Additionally, a successful synthetic strategy to the macrocyclic core would provide an excellent platform for further analog synthesis and structure activity relationship plotting.

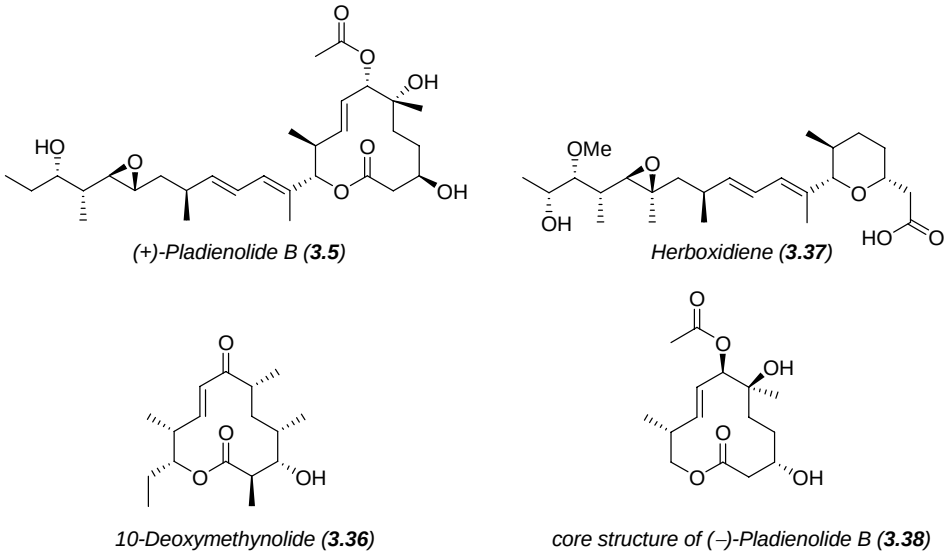
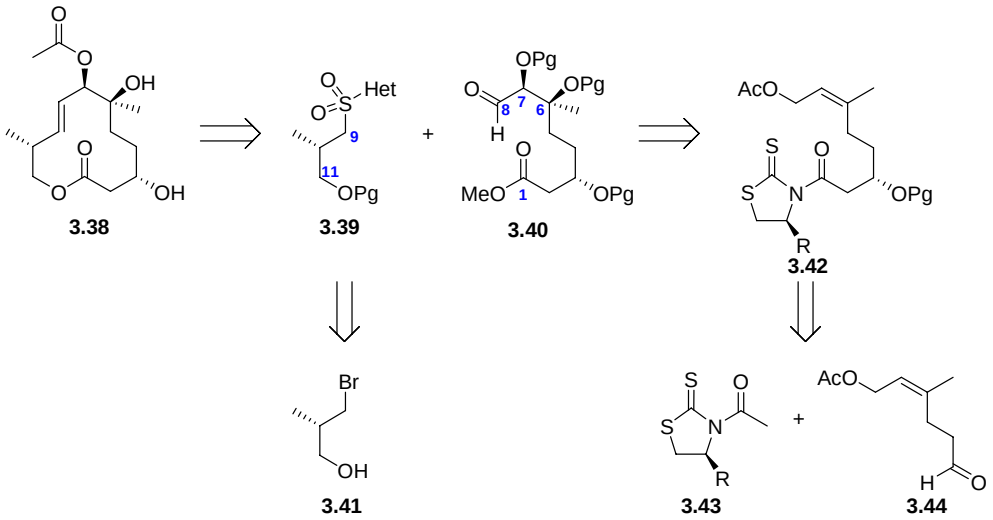


Figure 3.4 *Streptomyces* metabolites and projected core structure **3.38**.

In targeting the core structure **3.38** we sought to install the stereogenic centers in a purely reagent controlled fashion allowing for maximum flexibility and access to all sixteen stereoisomers (Scheme 3.7). We envisioned cleavage of the 12-membered macrolide by scission of the C(1)-O ester bond and the C(8)-C(9) bond affording a C(9)-C(11) fragment **3.39** and a C(1)-C(8) fragment **3.40**. We expected that these fragments could be coupled employing Julia-Kocienski-olefination[233,243] and macrolactonization.



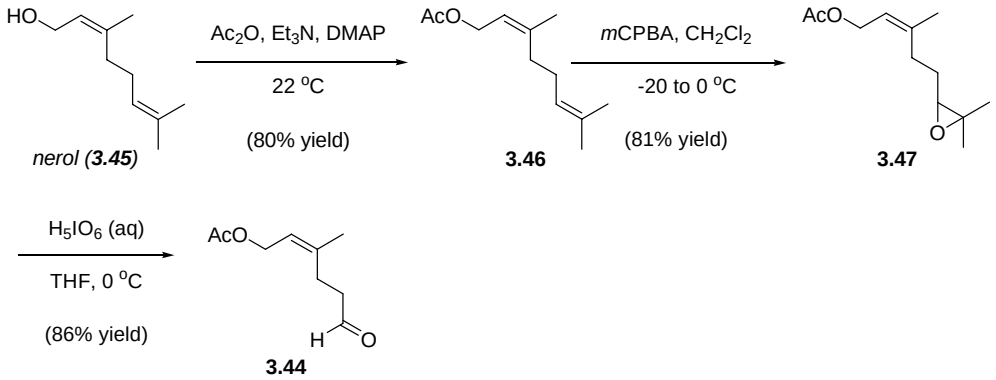
Scheme 3.7 Retrosynthesis of (–)-pladienolide B core (**3.38**).

The C(9)-C(11) fragment **3.39** could arise from the commercially available bromide **3.41**. Importantly, both enantiomers of this bromide are available. We anticipated that the vicinal oxygen-substituted stereocenters could be installed employing the Sharpless asymmetric dihydroxylation.[244] Key intermediate **3.42** would result from a chiral auxiliary-mediated acetate aldol condensation of an acetylthiazolidinethione[245] **3.43** and aldehyde **3.44**, ultimately available from nerol.

3.5 Preparation of the C(1)-C(8) Aldehyde Fragment

3.5.1 The Asymmetric Acetate Aldol Reaction[a]

Construction of the prerequisite aldehyde **3.44** became the first problem at hand (Scheme 3.8). The synthesis commenced from cheap and commercially available nerol (**3.45**). Initially nerol (**3.45**) was treated with acetic anhydride and triethylamine to give **3.46**. Acetate **3.46** was converted into epoxide **3.47** by exposure to *m*CPBA, which was subsequently opened and cleaved using aqueous periodic acid to furnish the desired aldehyde **3.44**.[246] This product was conveniently distilled in high yield.



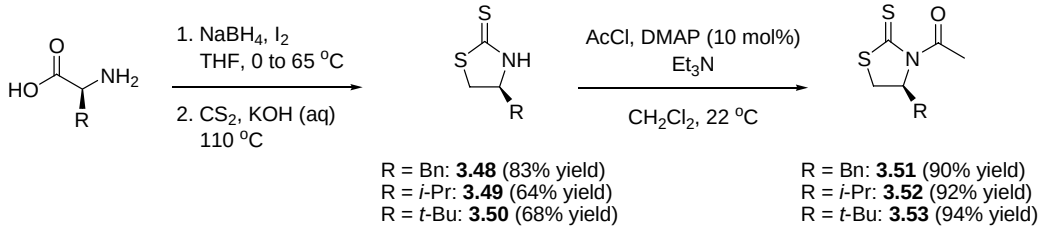
Scheme 3.8 Preparation of aldehyde **3.44**.

In efforts to install the hydroxy-substituted stereocenter at C(3) we recruited an auxiliary-mediated asymmetric acetate aldol reaction. The development of auxiliary-based asymmetric acetate aldol reactions have proven to be difficult[247] in comparison to the auxiliary-based diastereoselective propionate aldol reactions pioneered by Evans and co-workers.[248] The auxiliaries, such as Evan's *N*-oxazolidinones, which have provided excellent diastereoselectivities in various aldol additions, only afforded poor selectivities in the acetate aldol addition.[249] The diminished diastereoselectivity of the

[a] The research described in this chapter was conducted in collaboration with Dr. Philip R. Skaanderup.

acetate aldol reaction in comparison to the high level of diastereoselectivity attainable in propionate aldol reactions, has been attributed to the lack of α-substitution of the enolate, which is believed to be an important stereocontrol element.[250] Following pioneering work by Nagao and Fujita,[245] the research groups of Vilarrasa,[251,252] Crimmins,[250] and Sammakia[253,254] have shown that thiazolidinethione-based auxiliaries can overcome this impediment and furnish high level of diastereoselectivities in the acetate aldol addition.

A small library of thiazolidinethione auxiliaries were prepared in order to uncover suitable reaction conditions for the asymmetric acetate aldol reaction. Synthesis of the thiazolidinethione auxiliaries was readily accomplished from the corresponding amino acids (Scheme 3.9). Subjecting an amino acid to *in situ* generated borane furnished the corresponding amino alcohol,[255] which was smoothly converted to the corresponding thiazolidinethione (**3.48**, **3.49**, and **3.50**) upon exposure to a refluxing mixture of carbon disulfide and 2.0 M KOH.[256] Compounds **3.48** and **3.49** were easily recrystallized from ethanol and diethyl ether, respectively, while **3.50** had to be purified using silica-gel chromatography. These auxiliaries were subsequently acylated with acetyl chloride in the presence of triethylamine furnishing **3.51**, **3.52**, and **3.53** in excellent yields. Notably, both **3.52** and **3.53** were viscous oils while **3.51** was readily recrystallized from ethanol on > 20 gram scale.

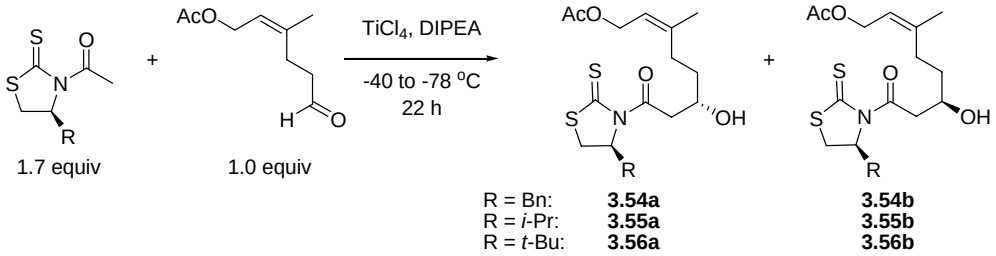


Scheme 3.9 Synthesis of thiazolidinethione auxiliaries.

After screening a range of different tertiary amine bases including triethylamine, (–)-sparteine and TMEDA in combination with titanium tetrachloride for enolization of the thiazolidinethione auxiliaries, we found that diisopropylethylamine (Hünig's base) provided superior yields and selectivities.[251] Treating the auxiliaries with titanium tetrachloride and Hünigs base at -40 °C followed by addition of aldehyde **3.44** gave the desired aldol condensation products **3.54-3.56** in good yields and with moderate diastereoselectivity (Table 3.2). Notably, the reaction had to be stirred at -78 °C for 22 h to reach full conversion. Previously Vilarrasa[251] reported that this type of

transformation had reached full conversion within ten minutes. A possible explanation for this significant rate difference could be competing coordination of the acetate group to the Lewis acid.

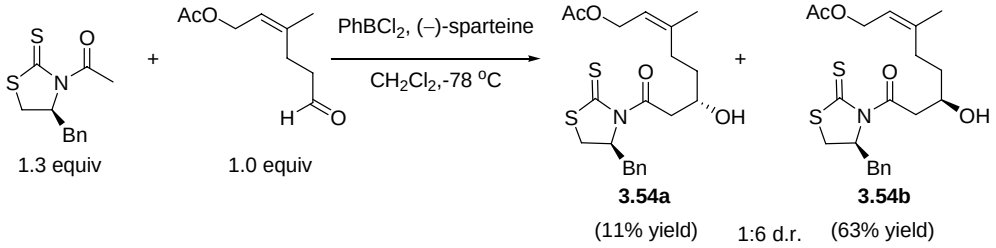
Table 3.2 Screening of thiazolidinethione auxiliaries.



entry	R	%yield (a)[a]	%yield (b)	%yield (a + b)	*dr* (a:b)
1	Bn	70	19	89	4:1
2	*i*-Pr	68	14	82	5:1
3	*t*-Bu	74	13	87	6:1

[a] Isolated yields.

Although both the valine **3.52** and the *tert*-leucine-derived **3.53** auxiliaries afforded slightly improved product ratios (entries 2 and 3), we settled for the phenylalanine-derived auxiliary, since all intermediates leading to **3.51** were highly crystalline allowing for easy purification during scale-up. Interestingly, if the enolate of **3.51** was generated from dichlorophenylborane and (–)-sparteine as disclosed by Sammakia.[253] **3.54b** was attained as the major product (Scheme 3.10). Hence, employing the same acetylthiazolidinethione **3.51** for diastereomeric control we were able to access either diastereomer **3.54a** or **3.54b** as the major product by fine-tuning the reaction conditions.[a]



Scheme 3.10 Accessing **3.54b** as the major product.

The observed selectivity in the titanium tetrachloride-mediated acetate aldol reaction can be explained by at least two different transition state models (Figure 3.5). Crimmins and co-workers[250]

[a] The absolute stereochemistry of **3.54b** was assigned using Mosher's ester analysis (Dale, A. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519). This experiment was carried out by Dr. Philip R. Skaanderup.

have invoked a highly ordered chelated transition state **3.57**. In this case the diastereoselectivity would arise from the preference of the R-group to adopt a pseudoequatorial position to avoid any 1,3-diaxial interactions with the auxiliary. In contrast, Evans[257] has suggested a boat-like transition state **3.58**, which is supported by semiempirical calculations reported by Houk and co-workers.[258]

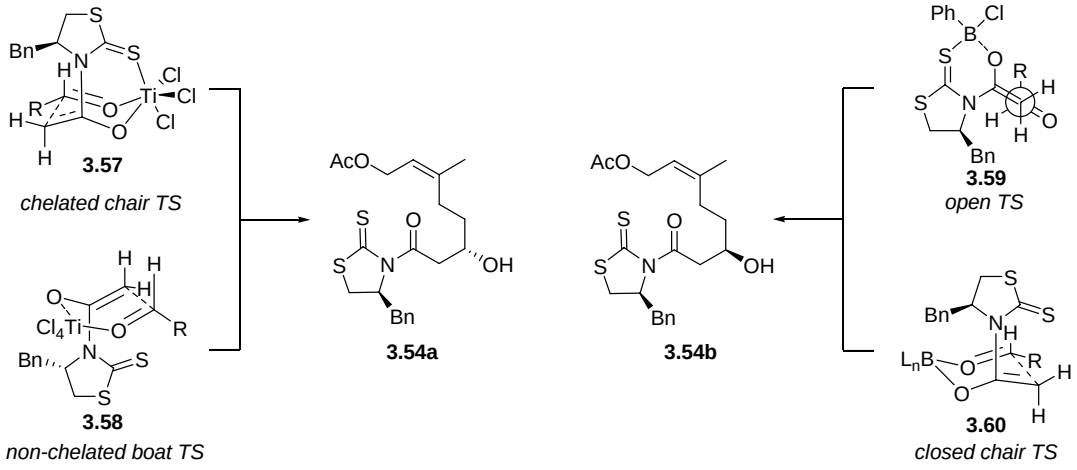


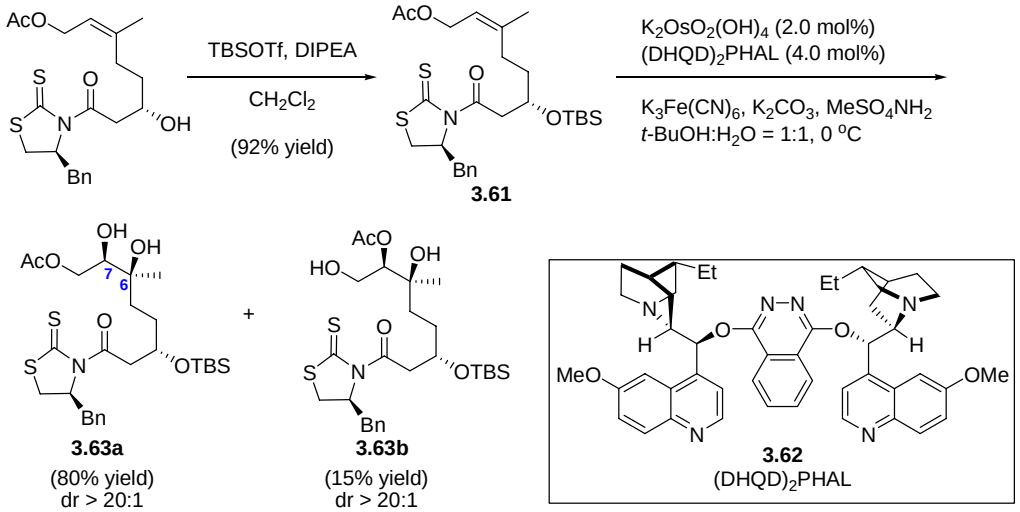
Figure 3.5 Possible models to account for the observed stereoselectivity.

Sammakia[253] have proposed the open transition state **3.59** to account for the stereochemistry in the dichlorphenylborane-mediate acetate aldol condensation. The closed chair transition state **3.60** may also be operative. The conformation of the closed transition state **3.60** can possibly be explained by a tendency to minimize the dipole interactions between the thiocarbonyl group of the auxiliary and the developing carbonyl of the aldolate.[253] However, this interpretation is possibly an oversimplification, since Evans[249] has shown that dipole effects are not a decisive stereochemical control element in the case of oxazolidinone auxiliary-mediated aldol reactions.

3.5.2 Installation of the C(7) and C(6) Stereocenters

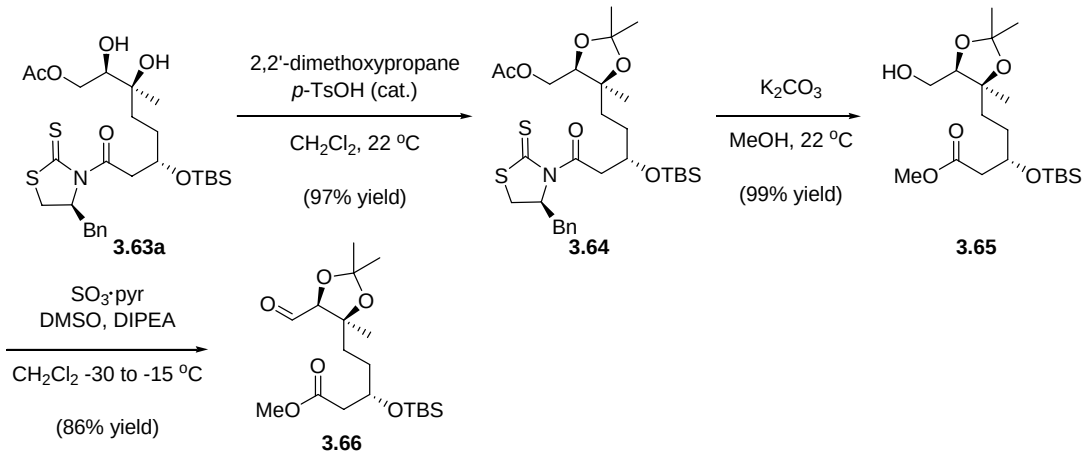
The successful execution of the acetate aldol reaction allowed us to focus on the diastereoselective installation of the C(6) and (7) hydroxy groups. To this end we decided to employ the Sharpless asymmetric dihydroxylation (Scheme 3.11).[244,259] After TBS-protection of the C(3) hydroxy group, compound **3.61** was exposed to standard Sharpless asymmetric dihydroxylation conditions using $(DHQD)_2PHAL$ (**3.62**) to induce stereoselectivity.[260] The desired diol **3.63a** was attained in 80% yield and greater than 20:1 diastereoselectivity at the newly formed stereocenters. Unfortunately, the secondary acetate **3.63b** was also formed in 15% yield and all attempts to convert this byproduct

into **3.63a** were unsuccessful. Nonetheless, we settled for these reaction conditions, since **3.63a** was produced with excellent diastereoselectivity and furthermore **3.63a** and **3.63b** were easily separated by silica-gel chromatography. The depicted stereochemistry was assigned employing Sharpless' empirical model (mnemonic device),[260] which has recently been updated by Norrby and co-workers.[261,a]



Scheme 3.11 Installation of the C(7) and C(6) hydroxy groups.

The key aldehyde fragment **3.66** was smoothly prepared from diol **3.63a** (Scheme 3.12). Treating **3.63a** with 2,2'-dimethoxypropane under acid conditions furnished acetonide **3.64** in excellent yield. Subsequent exposure to K_2CO_3 in methanol afforded acetate cleavage and concomitant methyl ester formation to provide the requisite primary alcohol **3.65**.



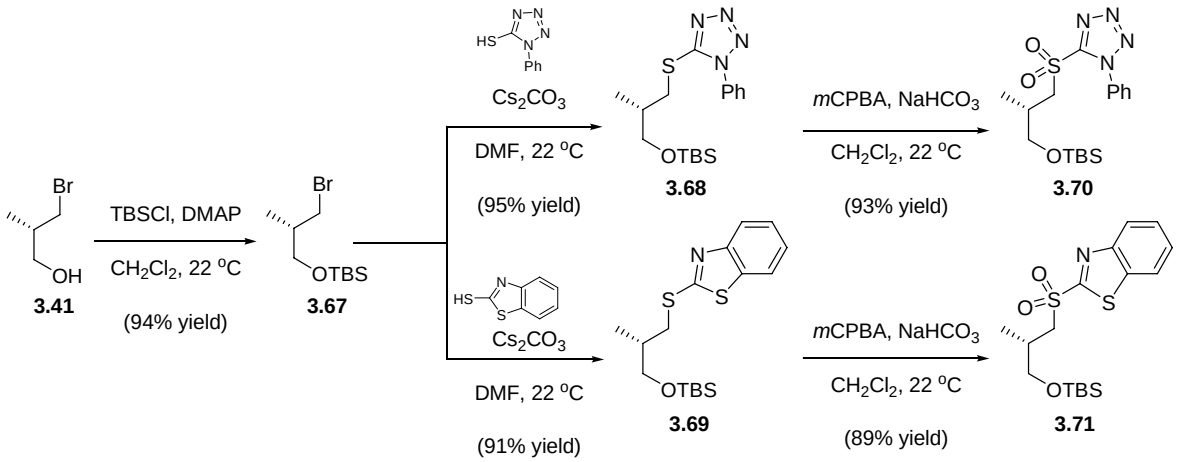
Scheme 3.12 Synthesis of the key C(1)-C(8) fragment **3.66**.

[a] This assignment was later confirmed by X-ray crystallography (cf. Chapter 3.8).

Subjecting the primary alcohol **3.65** to Parikh-Döring oxidation conditions gave aldehyde **3.66** in good yield. Aldehyde **3.66** could be purified using silica-gel chromatography without epimerization, however, in general it was used in its crude form.

3.6 The Julia-Kocienski-Olefination Approach to Fragment Coupling

Based on the seminal publications by Julia[243] and Kocienski[233] a one-pot alternative to the classical Julia-olefination,[262] namely the Julia-Kocienski olefination, has emerged as a powerful tool for advanced fragment linkage and olefin formation in total synthesis.[263,264] Our studies on the Julia-Kocienski-olefination began with the synthesis of C(9)-C(11) sulfone fragments **3.70** and **3.71** (Scheme 3.13). These sulfones were easily prepared from commercially available bromide **3.41**. Treating **3.41** with DMAP and TBSCl furnished **3.67** in excellent yield. The heterocyclic sulfones **3.70** and **3.71** were prepared from **3.67** by a two step *S*-alkylation/*S*-oxidation sequence. Alkyl bromide **3.67** was condensed with 1-phenyl-1*H*-tetrazole-5-thiol or 2-mercaptobenzothiazole in the presence of cesium carbonate affording the required sulfides **3.68** and **3.69** in high yield. These heteroarylthioethers **3.68** and **3.69** were easily oxidized to corresponding sulfone fragments **3.70** and **3.71** when exposed to *m*CPBA.

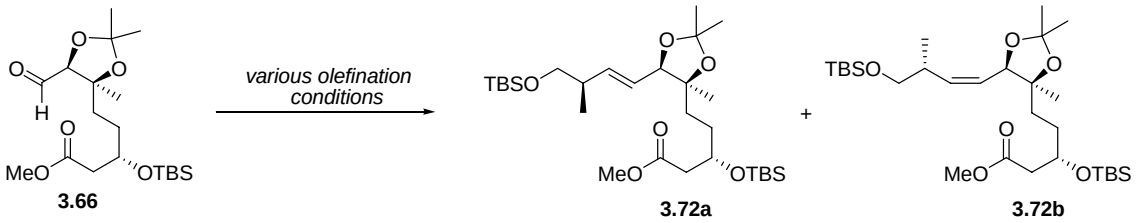


Scheme 3.13 Synthesis of the C(9)-C(11) sulfones **3.70** and **3.71**.

With **3.70** and **3.71** in hand, a careful survey of conditions for the fragment coupling was conducted (Table 3.3). It was found that deprotonating sulfone **3.70** with KHMDS followed by addition of aldehyde **3.66** under conditions reported by Kocienski[265] to furnish high *E*-selectivity gave an inseparable mixture of **3.72a** and **3.72b** (*E*:*Z* = 1:1) in low yield (entry 1). Ishigami[266] has recently

shown that adding 18-crown-6 led to improved levels of *E*-selectivity and yield. Unfortunately, in our case the yield and selectivity remained low under these reaction conditions (entry 2). Implementing very polar and strongly coordinating solvents for this transformation as described by Jacobsen[267] furnished the desired *E*-alkene exclusively, but in unsatisfactory yield (entry 3). Finally, it was attempted to implement sulfone **3.71** under reaction conditions disclosed by Ramachandran,[268] which provided good selectivity but low yield (entry 4).

Table 3.3 Attempted Julia-Kocienski olefination.



3.66 **3.72a** **3.72b**

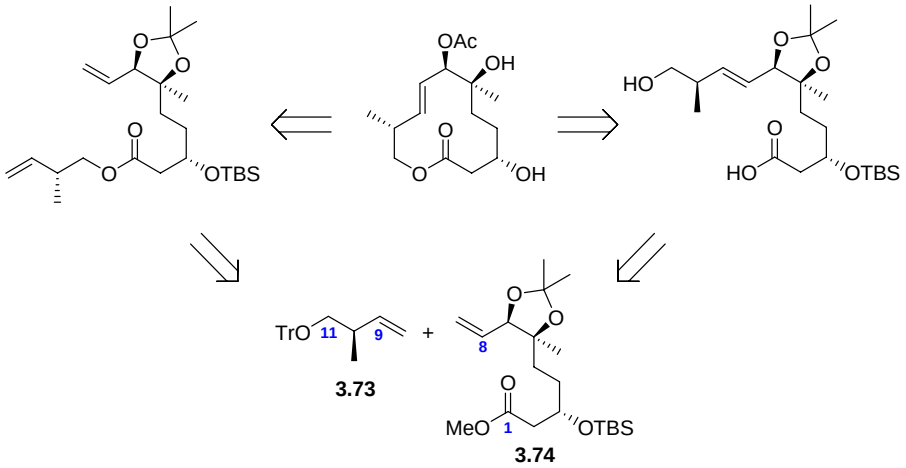
entry	sulfone	base/additive	solvent	T(°C)[a]	**3.72a** (*E*):**3.72b**(*Z*)[b]	% yield (**a+b**)[c]
1	**3.70**	KHMDS	DME	-78 to 22 °C	1:1	11
2	**3.70**	KHMDS/18-crown-6	THF	-78 to 22 °C	1:1	13
3	**3.70**	LiHMDS	DMF:DMPU = 1:1	-35 to 22 °C	*"E only"*	18
4	**3.71**	NaHMDS	DMF	-60 to 22 °C	8:1	23

[a] Base (1.05 equiv) and sulfone (1.1 equiv) was stirred at the indicated start temperature for 10 min. **3.66** (1.0 equiv) was added and then the mixture was allowed to warm to 22 °C (room temperature). [b] Determined by ^{1}H NMR analysis of the crude product mixtures. [c] Isolated yield, **3.72a** and **3.72b** were inseparable by silica-gel chromatography.

In all cases unreacted aldehyde **3.66** could be recovered from the reaction mixture, thus the low yield for this transformation may most likely be attributed to the highly congested sterical environment of aldehyde **3.66** as well as competing self-condensation of the sulfones. Further attempts to perform this transformation under Barbier-type conditions in order to limit potential self-condensation of the sulfones were fruitless.[264] The low yields of these reactions were detrimental to our synthetic endeavors toward the macrocyclic core of (–)-pladienolide B, hence we settled for alternative ways to install the C(8)-C(9) (*E*)-alkene.

3.7 The Metathesis-Esterification Approach

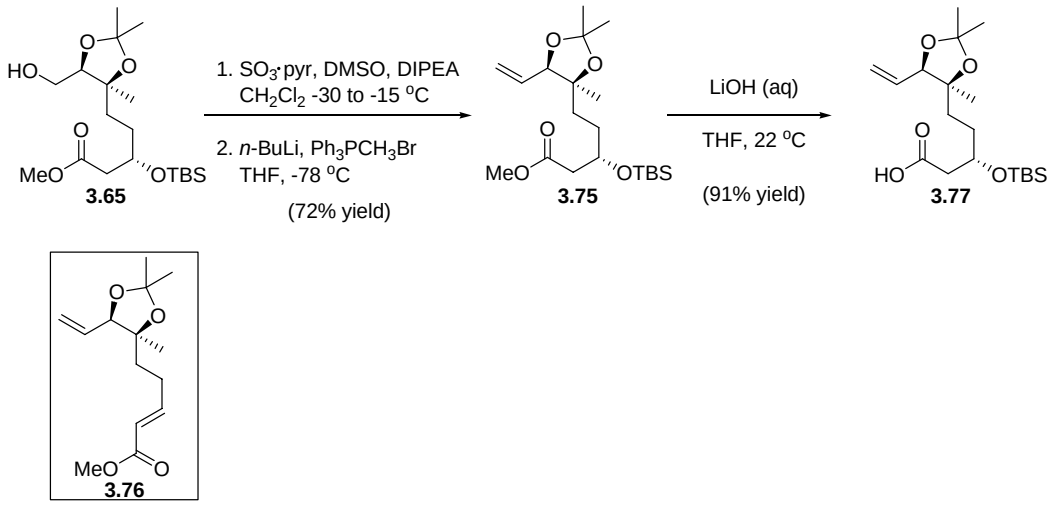
Two alternative strategies to the Julia-Kocienski-olefination approach were considered. We envisioned that the macrocyclic core **3.38** could arise from an esterification ring-closing metathesis sequence or through cross-metathesis followed by macrolactonization (Scheme 3.14). The requisite C(9)-C(11) coupling partner **3.73** would be available from commercial (*S*)-Roche ester, while the C(1)-C(8) fragment **3.74** could be attained from aldehyde **3.66** (cf. Scheme 3.11).



Scheme 3.14 Metathesis esterification approach to the macrocyclic core **3.38**.

3.7.1 The Esterification-Ring-Closing Metathesis Approach

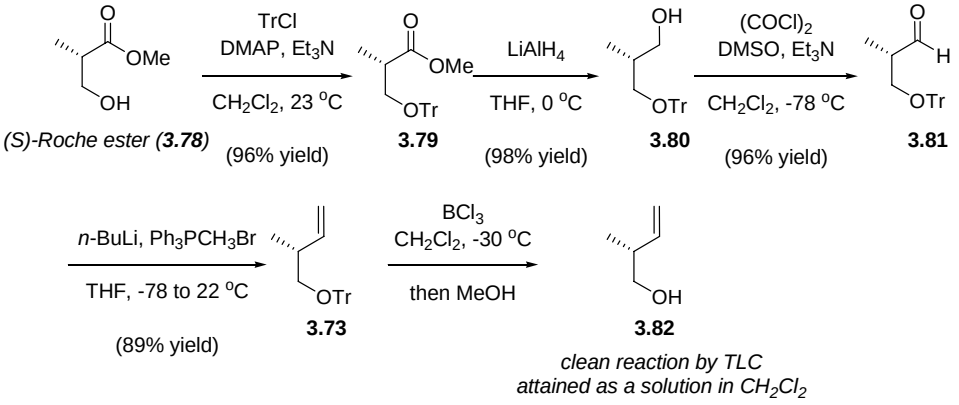
Preparation of the requisite acid **3.77** was achieved from alcohol **3.65** employing a three-step oxidation, Wittig methylenation, and ester hydrolysis sequence (Scheme 3.15).



Scheme 3.15 Preparation of acid **3.77**.

Significantly, aldehyde **3.66** had to be stirred with the phosphonium ylide at -78 °C for at least 12 h to reach full conversion. Premature warming to ambient temperature furnished low yields of the desired product **3.75**, likely due to competing deprotonation reactions. In some cases 5-10% of **3.76**, resulting from elimination of the OTBS-group, were isolated. Hydrolysis of methyl ester **3.75** gave **3.77** in excellent yield.

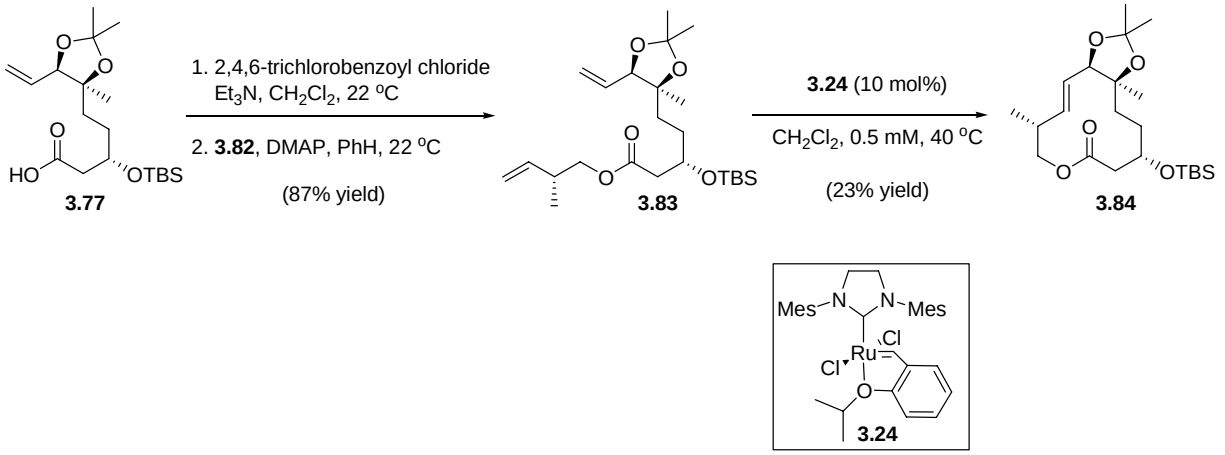
The alkene building block **3.82** was prepared from (*S*)-Roche ester (**3.78**) through a five-step sequence (Scheme 3.16). Initial tritylation followed by lithium aluminum hydride reduction, Swern oxidation, and Wittig methylenation afforded the tritylated alcohol **3.73** smoothly. Implementing BCl_3 followed by methanol[269] for deprotection of **3.73** cleanly generated the primary alcohol **3.82** by TLC, however, facile isolation of this compound was precluded due to the volatility of this compound. Hence, it was decided to use **3.82** as a solution in CH_2Cl_2 for the subsequent esterification reaction.



Scheme 3.16 Preparation of alkene building blocks **3.73** and **3.82**.

An esterification reaction between acid **3.77** and alcohol **3.82** utilizing the protocol of Yamaguchi and co-workers[232] afforded the bis terminal olefin **3.83** in good yield (Scheme 3.17). Next, the key RCM reaction was investigated. After surveying a range of different RCM-conditions we found that the macrocycle **3.84** could be obtained in 23% yield when exposed to Hoveyda-Grubbs' 2nd generation catalyst[145] **3.24** in refluxing dichloromethane under highly dilute conditions. Several unidentified products, likely resulting from dimerization and isomerization[163,164] of the double bonds were observed by TLC. The sterically demanding nature of the C(8) alkene, the presence of an allylic methyl group[270] as well as the potential chelation of the catalyst to the ester moiety[169-172] can

explain the difficulties associated with this RCM. Additionally, several other groups have reported limited success in forming 12-membered rings utilizing RCM.[271,272]



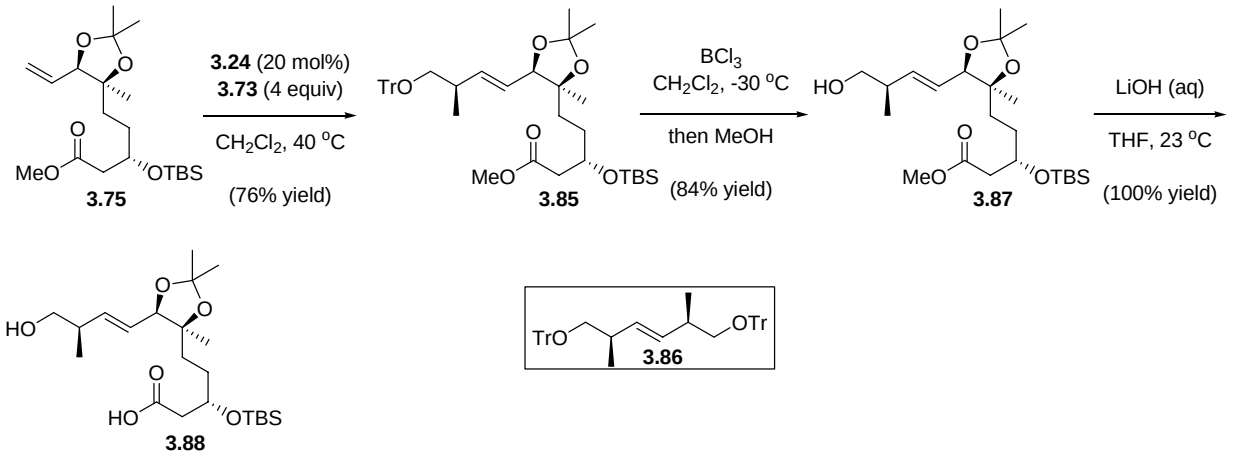
Scheme 3.17 RCM approach to macrocycle **3.84**.

Concurrent with our efforts toward implementing the esterification-RCM approach we had initiated investigations on a cross-metathesis macrolactonization sequence to couple the C(9)-C(11)-fragment **3.73** and forge the 12-membered macrocycle. Recognizing that the RCM would require extensive optimization to provide meaningful yields of the desired macrocycle, combined with the achievement of positive results in our cross-metathesis approach (cf. Chapter 3.7.2) led us to pursue the latter strategy.

3.7.2 The Cross Metathesis-Macrolactonization Approach

With **3.73** and **3.75** in hand we set out to investigate the cross-metathesis macrolactonization sequence to form the C(8)-C(9) *E*-olefin and forge the 12-membered macrocycle (Scheme 3.18). At the outset of our coupling studies, a number of conditions were tested with limited success. Treating **3.75** with 10 mol% of Grubbs' 2nd generation-catalyst[143] or Hoveyda-Grubbs' 2nd generation-catalyst[145] and two equivalents of **3.73** in refluxing dichloromethane furnished less than 30% of the desired alkene. However, two important observations from these experiments were encouraging; **3.75** was not undergoing homodimerization, and only the (*E*)-alkene **3.85** was being formed from **3.75**. In addition we found that **3.73** underwent homodimerization to furnish **3.86** on prolonged stirring. In an attempt to avoid competing dmierization of **3.73**, we decided to use **3.86** for the cross-metathesis reaction in combination with the more stable Hoveyda-Grubbs' 2nd generation catalyst. This approach was met with little success, since **3.86** was only slowly participating in the desired

CM-process. Finally, it was attempted to add four equivalents of **3.86** in two portions over the course of the reaction. Moreover, the catalyst loading was increased to 20 mol% of Hoveyda-Grubbs 2nd generation catalyst (added in three portions). Satisfyingly, this afforded the desired (*E*)-alkene **3.85** in 76% yield. With this result at hand we decided to venture forward eager to explore the key macrolactonization.

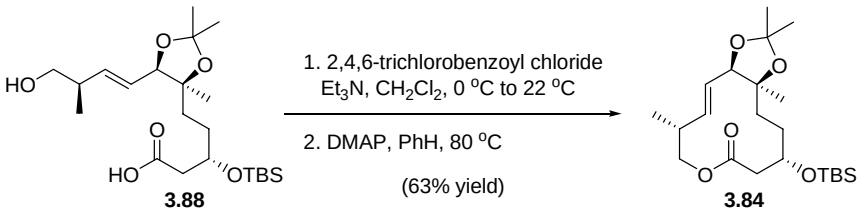


Scheme 3.18 Synthesis of *seco*-acid **3.88**.

As a prelude to the macrolactonization we had to selectively unmask the trityl protected hydroxy group and hydrolyse the methyl ester functionality. Conventional protocols for selective removal of the trityl blocking group using formic acid in ether[273] or diethyl aluminium chloride in dichloromethane[274] were unsatisfactory and led to multiple byproducts possibly resulting from competing desilyation and/or acetonide cleavage. Therefore we employed BCl_3 in combination with methanol, which has been reported by Jones[269] to selectively cleave trityl-ethers in the presence of silyl-protecting groups. Gratifyingly, when **3.85** was treated with BCl_3 at -30 °C followed by quenching with methanol **3.87** was obtained cleanly in 84% yield. Subsequent methyl ester hydrolysis using lithium hydroxide furnished the prerequisite *seco*-acid **3.88** in quantitative yield.

In order to close the macrocycle we settled for the Yamaguchi-protocol, which has proved itself to be an excellent methodology for performing macrolactonizations in numerous total syntheses.[275] In the classical procedure a mixed anhydride is preformed between 2,4,6-trichlorobenzoyl chloride and a *seco*-acid in tetrahydrofuran in the presence of triethylamine. After filtration of the NEt_3-HCl salt, the mixed anhydride is added slowly to a highly diluted solution of DMAP in toluene or benzene at

reflux.[232] A popular modification of this protocol was developed by Yonemitsu.[276] Yonemitsu observed that the direct addition of a large excess of DMAP to a highly dilute solution of the preformed mixed anhydride, generally at ambient temperature, afforded macrolactonization in high yield. Two advantages of this "modified" Yamaguchi protocol are that slow addition of the mixed anhydride is unnecessary and the milder reaction conditions (room temperature vs. reflux in benzene or toluene). Initially we attempted to close the macrocycle using the "modified" Yamaguchi procedure, which presented the mildest reaction conditions. Although a rapid reaction was taking place affording rapid conversion of the mixed anhydride, the desired macrolactone **3.84** was only isolated in a moderate 34% yield (Scheme 3.19).[a] Therefore we decided to implement the classical Yamaguchi-protocol. We found that adding the preformed mixed anhydride slowly over one hour to a refluxing solution of DMAP in benzene furnished the desired macrolactone in 63% yield (final cyclization concentration 0.0004 M). Neither an increase in the reaction temperature by switching to toluene nor a decrease in reaction temperature improved this yield.

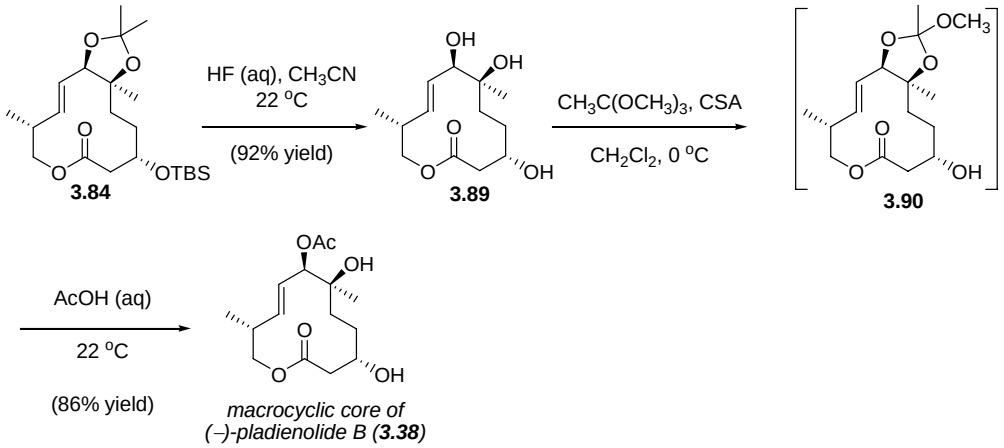


Scheme 3.19 Macrolactonization.

3.8 Completion of the Macrocyclic Core of (–)-Pladienolide B

With the prerequisite macrolactone **3.84** at hand we investigated ways to concomitantly remove the acetonide and TBS groups (Scheme 3.20). Initially we attempted to subject **3.84** to different mixtures of THF, AcOH, H_2O at room temperature or 50 °C. Even after prolonged heating *i.e.* 48 h at 50 °C only low conversion was observed. Therefore we decided to implement deblocking conditions previously deployed by Nicolaou and co-workers[277] in their total synthesis of the kinamycins. In the event, macrolactone **3.84** was dissolved in acetonitrile at room temperature and treated with aqueous HF furnishing the desired triol **3.89** in excellent yield.

[a] The major byproducts from this reaction are likely oligomers/dimers.



Scheme 3.20 Completion of the macrocyclic core of (–)-pladienolide B (**3.38**).

Having finally arrived at triol **3.89** the completion of the macrocyclic core structure of (–)-pladienolide B required differentiation between the C(3), C(6), and C(7) hydroxy groups. This was easily achieved by treating triol **3.89** with trimethyl orthoacetate and CSA followed by cleavage of the putative cyclic orthoester **3.90** with aqueous acetic acid. The exquisite regioselectivity of this acetylation is most likely caused by a propensity to place the acetyl-group on the sterically less congested secondary hydroxy group at C(7). Satisfyingly, we were able to attain X-ray quality crystals of **3.38** by recrystallization from diisopropylether (DIPE) and methanol. Thus based on the known stereochemistry of coupling fragment **3.73**, which relates back to the (*S*)-Roche ester, the structure and absolute stereochemistry of the (–)-pladienolide B core **3.38** was unambiguously assigned by single-crystal X-ray crystallography (Figure 3.6). Gratifyingly, this result verifies the absolute stereochemistry that was previously assigned by Mosher ester analysis (the acetate aldol) and by analogy (the Sharpless asymmetric dihydroxylation).

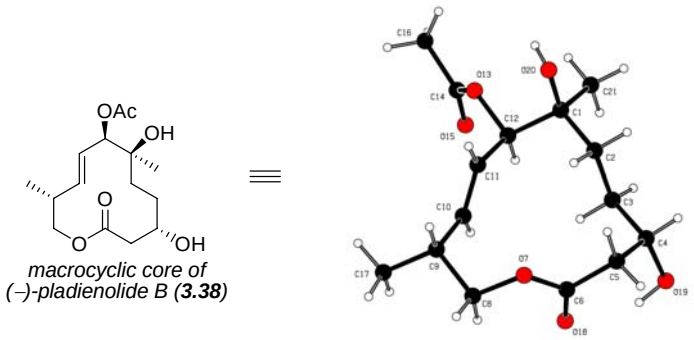
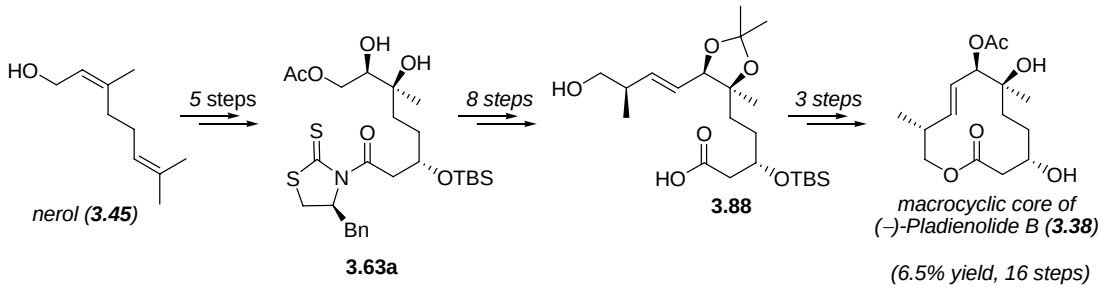


Figure 3.6 X-ray crystal structure of the macrocyclic core of (–)-pladienolide B (**3.38**).

The triol **3.89** and the (–)-pladienolide B core **3.38** were tested against a cancer cell line proliferation assay. To our disappointment these compound exhibited no activity. This can possibly be ascribed to the fact that we have targeted the enantiomeric core of (+)-pladienolide B (**3.5**). However, recent studies by Webb[278] on (+)-pladienolide B (**3.5**) inspired compounds have shown that both the epoxy group and carbonyloxy are key pharmocophoric elements. Moreover, an appropriately constrained linker to impart a proper conformational presentation of the functional groups was crucial to obtain biological activity. In combination with our observations this seems to suggest that the side-chain moiety is essential for potent anticancer activity.

3.9 Summary

Hitherto the project has culminated in an efficient synthesis of the macrocyclic core of (–)-pladienolide B (**3.38**) *i.e.* the enantiomer of the (+)-pladienolide B core (Scheme 3.21). The macrocyclic core **3.38** was achieved in 16 steps and 6.5% overall yield starting from nerol. The synthesis relied on a chiral auxiliary-mediated asymmetric aldol addition and the Sharpless asymmetric dihydroxylation to install the three oxygen substituted stereocenters at C(3), C(6), and C(7). The macrocyclic core was forged using an (*E*)-selective cross-metathesis followed by Yamaguchi-macrolactonization. The C(7) acetyl group was efficiently installed utilizing orthoester ring-opening. Unfortunately, this structure **3.38** exhibited no anti-cancer activity.



Scheme 3.21 Synthesis of the macrocyclic core of (–)-pladienolide B.

While this synthesis has targeted the enantiomeric core of (+)-pladienolide B it still retains its validity, since the strategy is purely reagent controlled. Thus the knowledge gathered throughout these studies can easily be applied in the synthesis of both the macrocyclic core of (+)-pladienolide B as well as more advanced analogs. Unfortunately, time constraints precluded the author from pursuing these intriguing aspects of the project.

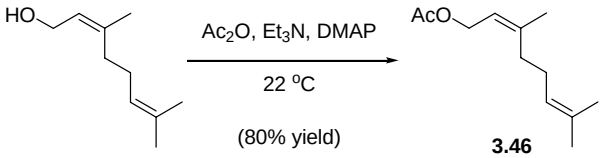
3.10 Experimental

3.10.1 Materials and Methods

See chapter 2.7.1 for general experimental information.

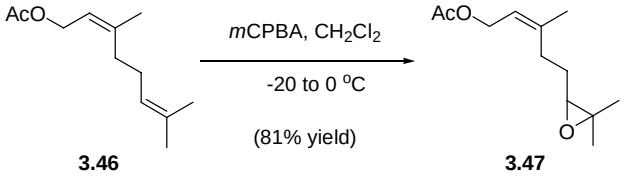
3.10.2 Synthesis of the Macrocyclic Core of (–)-Pladienolide B

Neryl Acetate (3.46)



To a stirred solution of nerol (57 mL, 0.32 mol) in CH_2Cl_2 (150 mL) was added Et_3N (89 mL, 0.64 mol) and DMAP (1.0 g, 8.2 mmol) followed by dropwise addition of Ac_2O (45 mL, 0.48 mol). The reaction mixture was stirred at 22 °C for 1 h then diluted with Et_2O (800 mL). The mixture was washed with saturated aqueous $CuSO_4$ (3 x 200 mL), H_2O (150 mL), and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a pale yellow oil. The crude oil was distilled (bp 89-90 °C, 1 mbar lit. bp.[279] 136-140 °C, 60 mbar) to afford **3.46** (50.1 g, 80% yield) as a colorless oil: R_f = 0.56 (heptane:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (dq, *J* = 7.3, 1.4 Hz, 1H), 5.11-5.05 (m, 1H), 4.55 (dq, *J* = 7.3, 0.9 Hz, 2H), 2.16-2.04 (m, 4H), 2.04 (s, 3H), 1.77-1.75 (m, 3H), 1.67 (d, *J* = 0.9 Hz, 3H), 1.59 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.0, 142.6, 132.1, 123.4, 119.0, 61.0, 32.1, 26.5, 25.6, 23.4, 21.0, 17.6; IR (film) 2968, 2932, 1742, 1733, 1447, 1377, 1234, 1023, 956, 826. Spectral data are in accordance with literature values.[280]

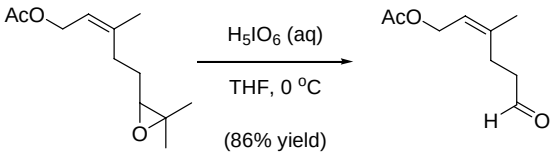
Acetic acid (*Z*)-5-(3,3-dimethyl-oxiranyl)-3-methyl-pent-2-enyl ester (3.47)



Acetate **3.46** (20.0 g, 0.102 mol) was dissolved in CH_2Cl_2 (100 mL) and cooled to -20 °C using a MeOH/ice bath. *m*CPBA (27.6 g, 0.112 mol, ~70% pure) as a suspension in CH_2Cl_2 (400 mL) was added over 2 h keeping the internal temperature below -5 °C. The cooling bath was removed and the mixture was stirred for an additional 2 h at 22 °C. The mixture was cooled to 0 °C using an ice/water bath, $Ca(OH)_2$ (31 g, 0.42 mol) was added, and the suspension was stirred for an additional 30 min.

The resulting suspension was filtered and the filter cake was washed with CH_2Cl_2 (250 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford an oil. The crude oil was distilled (bp 108-110 °C, 3 mbar, lit. bp.[279] 108-110° C, 2.7 mbar) to afford **3.47** (17.6 g, 81% yield) as a colorless oil: R_f = 0.27 (heptane:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.39 (t, *J* = 7.3 Hz, 1H), 4.57 (d, *J* = 7.3 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.24 (t, *J* = 7.8 Hz, 2H), 2.0 (s, 3H), 1.78-1.77 (m, 3H), 1.73-1.54 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.0, 141.7, 119.7, 63.7, 60.8, 58.3, 28.8, 27.5, 24.8, 23.4, 21.0, 18.7; IR (film) 2964, 1740, 1458, 1379, 1236, 1119, 1024, 956, 866, 68. Spectral data are in accordance with literature values.[246]

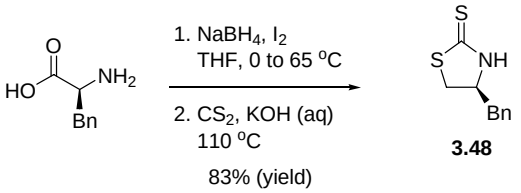
Acetic acid (*Z*)-3-methyl-6-oxo-hex-2-enyl ester (3.44)



3.47 **3.44**

Epoxide **3.47** (10.3 g, 0.048 mol) was dissolved in THF (100 mL), cooled to 0 °C using an ice/water bath, and a solution of H_5IO_6 (13.2 g, 0.058 mol) in water (100 mL) was added in a dropwise manner over 30 min. The mixture was stirred at 0 °C for an additional 4 h. The mixture was diluted with Et_2O (300 mL), washed with brine (2 x 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless oil. The crude oil was distilled (bp 89-90 °C, 1 mbar, lit. bp.[5] 102-105 °C, 2.7 mbar) to afford **3.44** (7.0 g, 86% yield) as a colorless oil: R_f = 0.18 (heptane:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.4 Hz, 1H), 5.42-5.36 (m, 1H), 4.58-4.56 (m, 2H), 2.58-2.52 (m, 2H), 2.45-2.39 (m, 2H), 2.04 (s, 3H), 1.75 (dt, *J* = 1.0, 2.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.4, 171.0, 140.4, 120.5, 60.7, 42.1, 24.3, 23.1, 21.0; IR (film) 2969, 2729, 1734, 1448, 1380, 1236, 1025, 959. Spectral data are in accordance with literature values.[246]

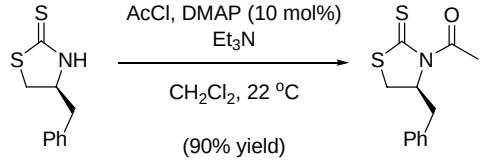
(*S*)-4-Benzylthiazolidine-2-thione (3.48)



$NaBH_4$ (16.4 g, 0.43 mol) was suspended in THF (500 mL) and the mixture was cooled to 0 °C while stirring. L-Phenylalanine (30.0 g, 0.18 mol) was added in one portion. I_2 (45.5 g, 0.18 mol) was dissolved in THF (150 mL) and added dropwise over 1 h by use of addition funnel resulting in vigorous evolution of hydrogen. After addition of the iodine solution was complete and the gas evolution had ceased the ice/water bath was removed, the mixture heated to reflux for 20 h, and then allowed to cool to ambient temperature. MeOH (~300 mL) was added until the mixture became clear. After 1 h stirring the mixture was concentrated under reduced pressure and the resulting white paste was dissolved by addition of 2.0 M NaOH (300 mL). The solution was stirred for 8 h and extracted with CH_2Cl_2 (3 x 500 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the desired product as a white powder (27.2 g, quantitative). The crude product was used without further purification.

(*S*)-2-Amino-3-phenylpropan-1-ol (30.0 g, 0.198 mol) was suspended in aqueous KOH (2.0 M, 500 mL). Carbon disulfide (76.1g, 60.6 mL, 1.0 mol) was added to the suspension, and the mixture was heated to reflux for 14 h. The resulting bright orange suspension was allowed to cool to ambient temperature. The reaction mixture was extracted with CH_2Cl_2 (3 x 500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product as a white solid. Recrystallization from EtOH afforded **3.48** (34.6 g, 83% yield) as white needles: mp 88-89 °C (EtOH), lit. mp[281] 79-80 °C (hexanes, ethyl acetate); R_f = 0.5 (CH_2Cl_2); $[\alpha]^{23}_D$ = -118 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.38-7.19 (m, 5H), 4.51-4.41 (m, 1H), 3.58 (dd, *J* = 11.2, 7.7 Hz, 1H), 3.31 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.04 (dd, *J* = 13.5, 7.6 Hz, 1H), 2.97 (dd, *J* =13.5, 6.6 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 200.8, 135.7, 129.0, 128.9, 127.4, 65.0, 39.9, 38.1; IR (KBr) 3145, 2939, 1494, 1457, 1440, 1342, 1294, 1267, 1192, 1160, 1075, 1046, 1030, 971, 951, 747, 735, 695, 658, 647. Spectral data are in accordance with literature values.[281]

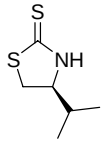
1-((*S*)-4-Benzyl-2-thiooxothiazolidin-3-yl)ethanone (3.51)



3.48 **3.51**

Thiazolidinethione **3.48** (19.0 g, 90.8 mmol), DMAP (1.12 g, 9.08 mmol), and Et_3N were dissolved in CH_2Cl_2 (250 mL) and cooled to 0 °C while stirring on an ice/water bath. AcCl (9.7 mL, 136 mmol) was added dropwise to the stirred solution and the resulting yellow solution was allowed to warm to 22 °C. The reaction mixture was stirred at 22 °C for 14 h, quenched with saturated aqueous NH_4Cl (50 mL) and diluted with Et_2O (750 mL). The organic phase was washed with saturated aqueous $CuSO_4$ (3 x 200 mL), H_2O (200 mL), and brine (200 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product as a yellow solid. The crude product was recrystallized from EtOH to afford **3.51** (20.6 g, 90% yield) as yellow needles: mp 88-90 °C (EtOH); R_f = 0.12 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = +243 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 5.38 (dddd, *J* = 10.6, 6.7, 3.9, 0.4 Hz, 1H), 3.38 (ddd, *J* = 11.5, 7.2, 1.1 Hz, 1H), 3.22 (dd, *J* = 13.2, 3.8 Hz, 1H), 3.04 (dd, *J* = 13.3, 10.6 Hz, 1H), 2.89 (dd, *J* = 11.6, 0.4 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.5, 170.6, 136.4, 129.4, 128.8, 127.1, 68.1, 36.6, 31.7, 27.0; IR (KBr) 3027, 2962, 2919, 1705, 1493, 1455, 1443, 1432, 1410, 1364, 1338, 1317, 1277, 1213, 1177, 1135, 1086, 1059, 1021, 1002, 955, 925, 898, 847, 750, 706, 672. Spectral data are in accordance with literature values.[282]

(*S*)-4-Isopropyl-thiazolidine-2-thione (3.49)

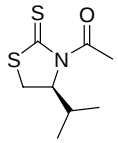


3.49

Prepared by the typical method employing L-valine (2.27 g, 0.019 mol). The crude product was recrystallized from Et_2O to afford **3.49** (2.01 g, 64% yield) as a white solid: mp 71-73 °C (Et_2O), lit. mp[256] 66-67 °C; R_f = 0.73 (EtOAc); $[\alpha]^{21}_D$ = -38.14 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 4.09-3.96 (m, 1H), 3.51 (dd, *J* = 11.1, 8.2 Hz, 1H), 3.32 (dd, *J* = 11.1, 8.5 Hz, 1H), 2.03-1.91 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.80 Hz, 3H); ^{13}C NMR (75.4 MHz,

$CDCl_3$) δ 200.7, 70.0, 35.6, 31.8, 18.7, 18.1; IR (film) 3146, 2961, 2872, 1492, 1391, 1372, 1314, 1272, 1191, 1163, 1094, 1040, 978, 661. Spectral data are in accordance with literature values.[256]

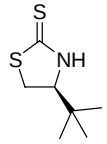
1-((*S*)-4-Isopropyl-2-thioxo-thiazolidin-3-yl)-ethanone (3.52)



3.52

Prepared by the typical method employing **3.49** (500 mg, 3.1 mmol). The crude product was purified using silica-gel chromatography (9:1 → 4:1, heptane-EtOAc) to afford **3.52** (579 mg, 92% yield) as a clear yellow oil: R_f = 0.53 (heptane:EtOAc = 4:1); $[\alpha]^{22}_D$ = +471.1 (*c* 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (ddd, *J* = 7.6, 6.2, 1.1 Hz, 1H), 3.51 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.02 (dd, *J* = 11.5, 1.2 Hz, 1H), 2.77 (s, 3H), 2.50-2.19 (m, 1H), 1.06 (d, *J* = 6.82 Hz, 3H), 0.98 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 203.2, 170.6, 71.2, 30.7, 30.3, 26.9, 19.0, 17.7; IR (film) 2963, 2933, 2875, 1696, 1468, 1411, 1366, 1307, 1245, 1207, 1099, 1074, 1033, 1009, 975, 858. Spectral data are in accordance with literature values.[283]

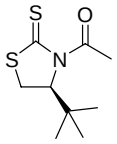
(*S*)-4-*tert*-Butyl-thiazolidine-2-thione (3.50)



3.50

Prepared by the typical method employing L-*tert*-leucinol (2.0 g, 0.0152 mol). The crude product was purified using silica-gel chromatography (CH_2Cl_2) to afford **3.50** (1.82 g, 68% yield) as a white solid: mp 133-135 °C (CH_2Cl_2), lit.[253] mp 140-141 °C; R_f = 0.46 (CH_2Cl_2); $[\alpha]^{22}_D$ = -43.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 4.02 (t, *J* = 8.8, 1H), 3.54-3.27 (m, 2H), 1.01 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.1, 73.5, 34.5, 34.2, 25.8; IR (film) 3151, 2959, 2903, 2870, 1504, 1474, 1293, 1236, 1202, 1074, 1042, 937. Spectral data are in accordance with literature values.[253]

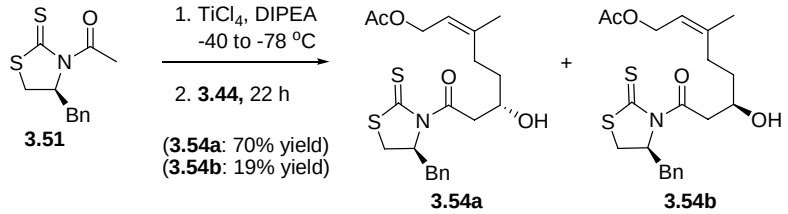
1-((*S*)-4-*tert*-Butyl-2-thioxo-thiazolidin-3-yl)-ethanone (3.53)



3.53

Prepared by the typical method employing **3.50** (500 mg, 2.85 mmol). The crude product was purified using silica-gel chromatography (4:1 → 1:1, heptane-EtOAc) to afford **3.53** (583.8 mg, 94% yield) as a clear yellow oil: R_f = 0.49 (heptane:EtOAc = 7:3); $[\alpha]^{23}_D$ = +566 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.53 (dd, *J* = 11.8, 8.4 Hz, 1H), 3.10 (dd, *J* = 11.8, 0.8 Hz, 1H), 2.77 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 205.2, 170.3, 71.9, 37.9, 30.4, 26.8, 26.7; IR (film) 2963, 2908, 2873, 1694, 1474, 1367, 1357, 1267, 1216, 1186, 1083, 1031, 1016. Spectral data are in accordance with literature values.[253]

Acetic acid (*Z*)-(*S*)-8-((*S*)-4-benzyl-2-thioxo-thiazolidin-3-yl)-6-hydroxy-3-methyl-8-oxo-oct-2-enyl ester (3.54a) and acetic acid (*Z*)-(*R*)-8-((*S*)-4-benzyl-2-thioxo-thiazolidin-3-yl)-6-hydroxy-3-methyl-8-oxo-oct-2-enyl ester (3.54b)

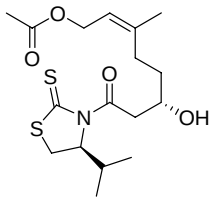


3.48 (10.0 g, 39.8 mmol) was dissolved in CH_2Cl_2 (250 mL) and cooled to -40 °C. $TiCl_4$ (4.5 mL, 41.0 mmol) was added dropwise to the resulting yellow solution followed by dropwise addition of diisopropylethylamine (7.13 mL, 41.0 mmol). The resulting dark red mixture was cooled to -78 °C and stirred for an additional 2 h. **3.44** (3.98 g, 23.4 mmol) was dissolved in CH_2Cl_2 (50 mL) and added dropwise to the reaction mixture. The mixture was stirred at -78 °C for an additional 20 h, quenched with a solution of saturated aqueous NH_4Cl (50 mL) and H_2O (50 mL), and diluted with Et_2O (500 mL). The organic phase was separated, washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product as a viscous yellow oil. The crude oil was purified using silica-gel chromatography (4:1 → 2:1, heptane-EtOAc) to afford **3.54a** (6.92 g, 70% yield) and **3.54b** (1.85 g, 19% yield), both as clear yellow oils.

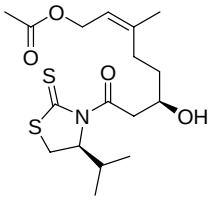
3.54a: R_f = 0.20 (heptane:EtOAc= 2:1); $[\alpha]^{23}_D$ = +159 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H), 5.41-5.34 (m, 2H), 4.69-4.50 (m, 2H), 4.17-4.01 (m, 1H), 3.59 (dd, *J* = 17.8, 2.5 Hz, 1H), 3.38 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.19 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.15 (dd, *J* = 17.8, 9.4, 1H), 3.02 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.99 (d, *J* = 4.0 Hz, 1H), 2.87 (d, *J* = 11.5, 1H), 2.41-2.25 (m, 1H), 2.25-2.12 (m, 1H), 2.04 (s, 3H), 1.75 (d, *J* = 0.8 Hz, 3H), 1.68-1.54 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.2, 172.7, 171.0, 141.8, 136.2, 129.3, 128.8, 127.1, 119.7, 68.2, 66.7, 60.9, 45.9, 36.6, 34.2, 31.9, 27.8, 23.2, 21.0; IR (film) 3505, 2934, 1735, 1691, 1443, 1364, 1259, 1241, 1162, 1039, 749, 703; HRMS (ESP+) calc'd for $C_{21}H_{27}NO_4Na$ ($[M+Na]^+$) 444.1275, found 444.1278.

3.54b: R_f = 0.24 (heptane:EtOAc= 2:1); $[\alpha]^{23}_D$ = +90 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 5.42-5.34 (m, 2H), 4.66-4.52 (m, 2H), 4.98-3.94 (m, 1H), 3.47 (dd, *J* =17.6, 9.1 Hz, 1H), 3.40-3.28 (m, 2H), 3.20 (dd, *J* = 13.2, 4.0 Hz, 1H), 3.02 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.89 (d, *J* = 11.6 Hz, 1H), 2.38-2.13 (m, 2H), 2.04 (s, 3H), 1.75 (d, *J* = 0.7 Hz, 3H), 1.68-1.50 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.3, 173.3, 170.9, 141.8, 136.2, 129.3, 128.8, 127.1, 119.6, 68.1, 67.3, 60.9, 45.5, 36.6, 34.4, 31.9, 27.7, 23.2, 21.0; IR (film) 3504, 3026, 2837, 1735, 1690, 1442, 1363, 1345, 1257, 1239, 1168, 1037; HRMS (ESP+) calc'd for $C_{21}H_{27}NO_4NaS_2$ ($[M+Na]^+$) 444.1275, found 444.1270.

Acetic acid (*Z*)-(*S*)-6-hydroxy-8-((*S*)-4-isopropyl-2-thioxo-thiazolidin-3-yl)-3-methyl-8-oxo-oct-2-enyl ester (3.55a) and acetic acid (*Z*)-(*R*)-6-hydroxy-8-((*S*)-4-isopropyl-2-thioxo-thiazolidin-3-yl)-3-methyl-8-oxo-oct-2-enyl ester (3.55b)



3.55a



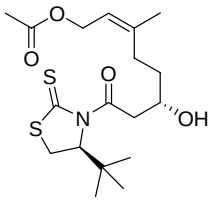
3.55b

Prepared by the typical method employing **3.52** (187 mg, 0.920 mmol) and **3.44** (92 mg, 0.54 mmol). The crude product was purified using silica-gel chromatography (4:1 → 2:1, heptane-EtOAc) to afford **3.55a** (137.2 mg, 68% yield) and **3.55b** (28.2 mg, 14% yield), both as clear yellow oils.

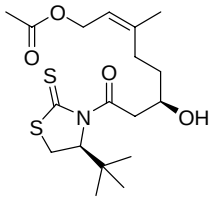
3.55a: R_f = 0.28 (heptane:EtOAc = 2:1); $[\alpha]^{23}_D$ = +286 (*c* 2.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.3, 7.3 Hz, 1H), 5.16 (ddd, *J* = 7.8, 6.3, 1.0 Hz, 1H), 4.71-4.45 (m, 2H), 4.18-3.96 (m, 1H), 3.61 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.52 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.15 (dd, *J* = 17.7, 9.3 Hz, 1H), 3.03 (dd, *J* = 11.5, 1.1 Hz, 1H), 2.98 (br s, 1H), 2.44-2.11 (m, 3H), 2.05 (s, 3H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.73-1.52 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 203.0, 172.8, 171.1, 142.0, 119.7, 71.3, 66.99, 61.0, 45.6, 34.3, 30.8, 30.5, 27.9, 23.3, 21.1, 19.0, 17.8; IR (film) 3529, 2964, 1735, 1700, 1443, 1364, 1240, 1169, 1091, 1038; HRMS (ESP+) calc'd for $C_{17}H_{27}NO_4NaS_2$ ($[M+Na]^+$) 396.1279, found 396.1257.

3.55b: R_f = 0.38 (heptane:EtOAc = 2:1); $[\alpha]^{23}_D$ = +193 (*c* 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.1 Hz, 1H), 5.18 (ddd, *J* = 7.7, 6.4, 1.0 Hz, 1H), 4.73-4.42 (m, 2H), 4.08-3.90 (m, 1H), 3.52 (dd, *J* = 11.5, 7.9 Hz, 1H), 3.48 (dd, *J* = 17.4, 9.3 Hz, 1H), 3.32 (dd, *J* = 17.4, 2.9 Hz, 1H), 3.04 (dd, *J* = 11.5, 1.1 Hz, 1H), 2.46-2.12 (m, 3H), 2.05 (s, 3H), 1.76 (d, *J* = 1.1 Hz, 3H), 1.73-1.48 (m, 2H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 203.1, 173.5, 171.1, 142.1, 119.7, 71.3, 67.6, 61.0, 45.3, 34.6, 30.7, 30.6, 27.9, 23.4, 21.1, 19.1, 17.8; IR (film) 3519, 2963, 2874, 1733, 1699, 1468, 1442, 1363, 1248, 1169, 1037; HRMS (ESP+) calc'd for $C_{17}H_{27}NO_4NaS_2$ ($[M+Na]^+$) 396.1279, found 396.1257.

Acetic acid (*Z*)-(*S*)-8-((*S*)-4-*tert*-butyl-2-thioxo-thiazolidin-3-yl)-6-hydroxy-3-methyl-8-oxo-oct-2-enyl ester (3.56a) and acetic acid (*Z*)-(*R*)-8-((*S*)-4-*tert*-butyl-2-thioxo-thiazolidin-3-yl)-6-hydroxy-3-methyl-8-oxo-oct-2-enyl ester (3.56b)



3.56a



3.56b

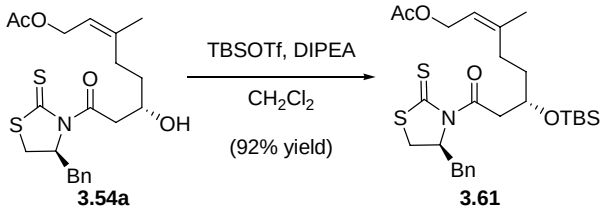
Prepared by the typical method employing **3.53** (200 mg, 0.920 mmol) and **3.44** (92 mg, 0.54 mmol). The crude product was purified using silica-gel chromatography (4:1 → 2:1, heptane-EtOAc) to afford **3.56a** (154.9 mg, 74% yield) and **3.56b** (27.2 mg, 13% yield), both as clear yellow oils.

3.56a: R_f = 0.17 (heptane:EtOAc = 7:3); $[\alpha]^{23}_D$ = +325 (*c* 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.3 Hz, 1H), 5.31 (d, *J* = 8.6 Hz, 1H), 4.81-4.45 (m, 2H), 4.18-3.92 (m, 1H), 3.58 (dd, *J* = 17.7, 2.5 Hz, 1H), 3.54 (dd, *J* = 11.8, 8.3 Hz, 1H), 3.15 (dd, *J* = 17.7, 9.2 Hz, 1H), 3.11 (d, *J* = 11.8 Hz, 1H), 3.04 (br s, 1H), 2.44-2.11 (m, 2H), 2.05 (s, 3H), 1.76 (s, 3H), 1.68-1.51 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 220.4, 172.3, 171.0, 142.0, 119.7, 72.0, 67.3, 61.0, 45.1, 37.8, 34.3, 30.5, 27.9, 26.8, 23.3, 21.0; IR (film) 3518, 2964, 2873, 1732, 1692, 1471, 1442, 1367, 1316, 1234, 1150, 1137, 10485, 976; HRMS (ESP+) calc'd for $C_{18}H_{29}NO_4NaS_2$ ($[M+Na]^+$) 410.1431, found 410.1446.

3.56b: R_f = 0.21 (heptane:EtOAc = 7:3); $[\alpha]^{23}_D$ = +305 (*c* 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.2 Hz, 1H), 5.34 (d, *J* = 8.4 Hz, 1H), 4.72-4.47 (m, 2H), 3.99 (dq, *J* = 7.8, 3.7 Hz, 1H), 3.54 (dd, *J* = 11.8, 8.3 Hz, 1H), 3.48 (dd, *J* = 17.4, 9.4 Hz, 1H), 3.32 (dd, *J* = 17.4, 2.8 Hz, 1H), 3.30 (d, *J* = 2.8 Hz, 1H), 3.11 (d, *J* = 11.8 Hz, 1H), 2.45-2.10 (m, 2H), 2.05 (s, 3H), 1.76 (s, 3H), 1.73-1.47 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 205.2, 172.8, 171.0, 142.0, 119.7, 72.1, 67.5, 61.0, 45.1, 37.9, 34.6, 30.5, 28.0, 26.8, 23.3, 21.0; IR (film) 3523, 2964, 1732, 1692, 1471, 1443, 1367, 1317, 1235, 1197, 1149, 1136, 1086, 1045, 1021; HRMS (ESP+) calc'd for $C_{18}H_{29}NO_4NaS_2$ ($[M+Na]^+$) 410.1431, found 410.1445.

.

Acetic acid (*Z*)-(*S*)-8-((*S*)-4-benzyl-2-thioxo-thiazolidin-3-yl)-6-(*tert*-butyl-dimethyl-silanyl-oxy)-3-methyl-8-oxo-oct-2-enyl ester (3.61)

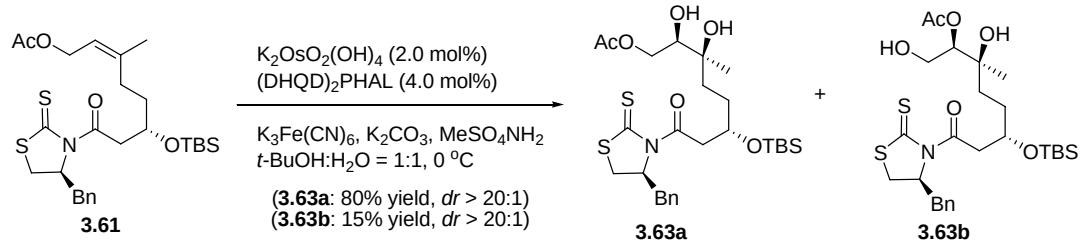


3.54a **3.61**

3.54a (3.42 g, 8.11 mmol) was dissolved in CH_2Cl_2 (50 mL) and the resulting clear yellow solution was cooled to -78 °C while stirring. A solution of diisopropylethylamine (2.1 mL, 12.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.6 mL, 11.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture. The mixture was stirred at -78 °C for 3 h, quenched with MeOH (10 mL), and allowed to warm to ambient temperature. The reaction mixture was diluted with Et_2O (300 mL), washed with H_2O (4 x 50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a yellow viscous oil. The crude product was purified using silica-gel

chromatography (19:1 → 4:1, heptane-EtOAc) to afford **3.61** (4.02 g, 92% yield) as a yellow oil: R_f = 0.33 (heptane:EtOAc = 6:1); $[\alpha]^{23}_D$ = +146 (*c* 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.13 (m, 5H), 5.32 (dt, *J* = 7.3, 0.9 Hz, 1H), 5.24 (ddd, *J* = 10.7, 6.9, 3.8 Hz, 1H), 4.52 (d, *J* = 7.3 Hz, 2H), 4.35-4.21 (m, 1H), 3.55 (dd, *J* = 16.7, 7.8 Hz, 1H), 3.31 (dd, *J* =11.5, 7.1 Hz, 1H), 3.23-3,14 (m, 2H), 3.00 (dd, *J* = 13.1, 10.6 Hz, 1H), 2.84 (d, *J* = 11.6 Hz, 1H), 2.43-2.00 (m, 2H), 2.00 (s, 3H), 1.73 (d, *J* = 0.9 Hz, 3H), 1.69-1.48 (m, 2H), 0.82 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.1, 171.9, 170.9, 142.6, 136.5, 129.4, 128.8, 127.1, 119.1, 68.8, 68.6, 60.8, 45.6, 36.4, 36.1, 32.1, 27.5, 25.7, 23.5, 21.0, 17.9, -4.4, -4.6; IR (film) 3026, 2954, 2931, 2855, 1735, 1701, 1472, 1364, 1234, 1164, 1041, 837, 777, 702; HRMS (ESP+) calc'd for $C_{27}H_{41}NO_4NaSiS_2$ ($[M+Na]^+$) 558.2144, found 558.2162.

Acetic acid (2*R*,3*S*,6*S*)-8-((*S*)-4-benzyl-2-thioxo-thiazolidin-3-yl)-6-(*tert*-butyl-dimethyl-silanyl-oxy)-2,3-dihydroxy-3-methyl-8-oxo-octyl ester (3.63a) and acetic acid (1*R*,2*S*,5*S*)-7-((*S*)-4-benzyl-2-thioxo-thiazolidin-3-yl)-5-(*tert*-butyl-dimethyl-silanyloxy)-2-hydroxy-1-hydroxymethyl-2-methyl-7-oxo-heptyl ester (3.63b)

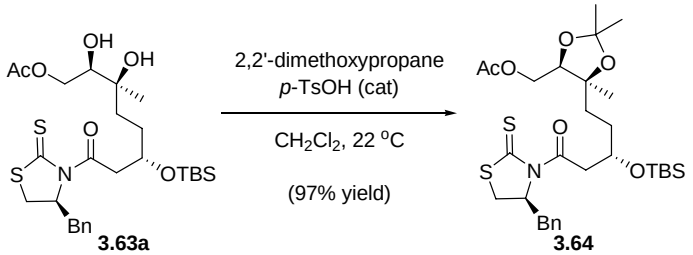


A mixture of potassium carbonate (1.52 g, 11.0 mmol), potassium hexacyanoferrate(III) (3.63 g, 11.0 mmol), methanesulfonamide (700 mg, 7.35 mmol), $K_2OsO_2(OH)_4$ (26.9 mg, 0.073 mmol), and $(DHQD)_2PHAL$ (115 mg, 0.147 mmol) in H_2O (15.0 mL) and *t*-BuOH (15.0 mL), was stirred at 22 °C for 15 min. The mixture was cooled to 0 °C and stirred for 15 min. **3.61** (1.98 g, 3.67 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and added to the reaction mixture in one portion. The mixture was stirred at 0 °C for 24 h, subsequently allowed to warm to ambient temperature, and quenched with Na_2SO_3 (500 mg). The reaction mixture was diluted with EtOAc (200 mL), washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a dark yellow viscous oil. The crude oil was purified using silica-gel chromatography (2:1, heptane-EtOAc) to afford **3.63a** (1.67 g, 80% yield) and **3.63b** (309 mg, 15% yield), both as bright yellow oils.

3.63a: R_f = 0.16 (heptane:EtOAc = 2:1); $[\alpha]^{23}_D$ = +103 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.05 (m, 5H), 5.28 (ddd, *J* = 10.7, 7.0, 4.0 Hz, 1H), 4.41-4.49 (m, 2H), 4.08 (dd, *J* = 11.6, 8.4 Hz, 1H), 3.69 (ddd, *J* = 8.3, 3.9, 2.4 Hz, 1H), 3.57 (dd, *J* = 16.9, 7.3 Hz, 1H), 3.35 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.31-3.18 (m, 2H), 3.03 (dd, *J* = 13.0, 10.7 Hz, 1H), 2.88 (d, *J* = 11.5 Hz, 1H), 2.11 (s, 3H), 1.81-1.55 (m, 3H), 1.50-1.37 (m, 1H); 1.21 (s, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.1, 171.9, 171.4, 136.5, 129.4, 128.9, 127.1, 75.7, 73.0, 69.1, 68.5, 65.9, 45.5, 36.5, 32.1, 32.0, 30.8, 25.7, 23.2, 20.9, 17.9, -4.3, -4.6; IR (film) 3504, 2955, 2929, 2856, 1743, 1690, 1452, 1363, 1257, 1169, 1046, 836, 775; HRMS (ESP+) calc'd for $C_{27}H_{43}NO_6NaSiS_2$ ($[M+Na]^+$) 592.2199, found 592.2196.

3.63b: R_f = 0.10 (Heptane:EtOAc = 2:1); $[\alpha]^{23}_D$ = +30.9 (*c* 0.31, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.14 (m, 5H), 5.22 (ddd, *J* = 10.8, 7.0, 4.0 Hz, 1H), 4,75 (t, *J* = 4.5 Hz, 1H), 4.34-4.23 (m, 1H), 3.91-3.73 (m, 2H), 3.50 (dd, *J* = 17.0, 7.3 Hz, 1H), 3.29 dd (11.5, 7.0 Hz, 1H), 3.24-3.09 (m, 2H), 2.96 (dd, *J* = 13.1, 10.6 Hz, 1H), 2.82 (d, *J* = 11.5 Hz, 1H), 2.08 (s, 3H), 1.74-1.39 (m, 4H), 1.13 (s, 3H), 0.79 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.2, 171.8, 171.0, 136.4, 129.4, 128.9, 127.2, 77.6, 73.9, 68.8, 68.5, 62.1, 45.4, 36.5, 33.7, 32.1, 30.7, 25.7, 23.3, 21.1, 18.0, -4.4, -4.6; IR (film) 3450, 2954, 2928, 2892, 2857, 1734, 1707, 1690, 1451, 1433, 1380, 1292, 1257, 1230, 1168, 1045, 835; HRMS (ESP+) calc'd for $C_{27}H_{43}NO_6NaSiS_2$ ($[M+Na]^+$) 592.2199, found 592.2196.

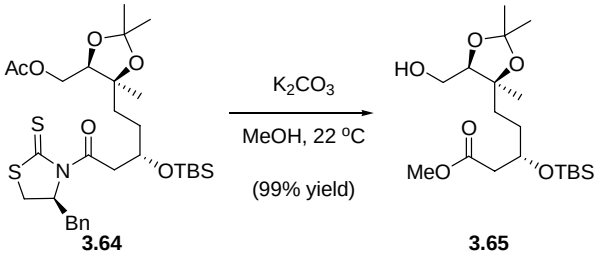
Acetic acid (4*R*,5*S*)-5-[(*S*)-5-((*S*)-4-benzyl-2-thioxo-thiazolidin-3-yl)-3-(*tert*-butyl-dimethyl-silanyloxy)-5-oxo-pentyl]-2,2,5-trimethyl-[1,3]dioxolan-4-ylmethyl ester (3.64)



3.63a (1.67 g, 2.9 mmol) was dissolved in CH_2Cl_2 (50 mL), 2,2-dimethoxypropane (7.2 mL, 59 mmol), and one grain of *para*-toluenesulfonic acid monohydrate were added while stirring. The resulting bright yellow solution was stirred at 22 °C for 30 min, diluted with Et_2O (250 mL), washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, and

concentrated *in vacuo* to afford a yellow viscous oil. The crude product was purified using silica-gel chromatography (2:1, heptane-EtOAc) to afford **3.64** (1.72 g, 97% yield) as a yellow oil: R_f = 0.68 (eluent: heptane:EtOAc = 1:1); $[\alpha]^{23}_D$ = +129 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.22 (m, 5H), 5.26 (ddd, *J* = 10.5, 6.8, 3.8 Hz, 1H), 4.44-4.30 (m, 1H), 4.25 (dd, *J* = 11.6, 3.9 Hz, 1H), 4.12 (dd, *J* = 11.6, 7.9 Hz, 1H), 3.97 (dd, *J* =7.9, 3.9 Hz, 1H), 3.56 (dd, *J* = 16.9, 7.9 Hz, 1H), 3.34 (dd, *J* = 11.6, 7.1 Hz, 1H), 3.29-3.20 (m, 1H), 3.18 (dd, *J* = 16.9, 4.0 Hz, 1H), 3.04 (dd, *J* = 13.1, 7.9 Hz, 1H), 2.88 (d, *J* = 11.6 Hz, 1H), 2.11 (s, 3H), 1.92-1.58 (m, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H), 1.26-1.16 (m, 1H), 0.85 (s, 9H), 0.09 (s. 3H), 0.05 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.1, 172.1, 170.8, 136.6, 129.4, 128.9, 127.2, 108.2, 81.7, 81.2, 69.1, 68.7, 62.5, 45.7, 36.5, 32.1, 31.0, 29.7, 28.3, 27.0, 25.8, 23.0, 20.9, 18.0, -4.4, -4.7; IR (film) 2932, 2856, 1744, 1701, 1457, 1370, 1231, 1167, 1044, 836, 776; HRMS (ESP+) calc'd for $C_{30}H_{47}NO_6NaSiS_2$ ($[M+Na]^+$) 632.2512, found 632.2490.

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-((4*S*,5*R*)-5-hydroxymethyl-2,2,4-trimethyl-[1,3]dioxolan-4-yl)-pentanoic acid methyl ester (3.65)

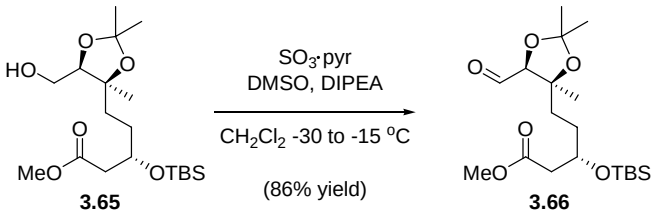


3.64 **3.65**

3.64 (1.51 g, 2.48 mmol) was dissolved in MeOH (100 mL) and K_2CO_3 (1.71 g, 12.4 mmol) was added while stirring at 22 °C. The bright yellow mixture became colorless within 5 minutes, and the mixture was stirred for an additional 1 h at 22 °C. The reaction mixture was diluted with Et_2O (200 mL), washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford an oil. The crude product was purified using silica-gel chromatography (4:1, heptane-EtOAc) to afford **3.65** (956 mg, 99% yield) as a colorless oil: R_f = 0.69 (EtOAc); $[\alpha]^{23}_D$ = +1.49 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15-4.05 (m, 1H), 3.93 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.80 (ddd, *J* = 11.9, 7.9, 4.1 Hz, 1H), 3.69 (dd, *J* = 7.6, 3.6 Hz, 1H), 3.66 (s, 3H), 2.51-2.36(m, 2H), 1.65-1.65 (m, 2H), 1.63-1.49 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H), 1.20-1.05 (m, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.1, 107.8, 84.7, 80.9, 69.5, 61.2, 51.5, 42.4, 30.9, 30.1, 28.3, 27.0, 25.7, 23.3, 17.9, -4.5, -4.9; IR (film) 3473, 2954, 2858, 1739, 1472,

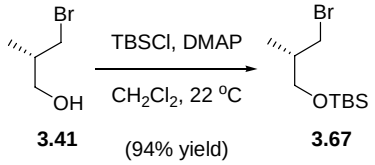
1463, 1436, 1378, 1315, 1217, 1054, 1005, 927, 897, 837, 812, 777, 710, 664; HRMS (ESP+) calc'd for $C_{19}H_{38}O_6NaSi$ ($[M+Na]^+$) 413.2331, found 413.2320.

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-((4*S*,5*S*)-5-formyl-2,2,4-trimethyl-[1,3]dioxolan-4-yl)-pentanoic acid methyl ester (3.66)



3.65 (708 mg, 1.81 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to -40 °C while stirring. Diisopropylethyl amine (1.2 mL, 7.25 mmol) and DMSO (1.5 mL) were added. SO_3·Pyr (866 mg, 5.44 mmol) was dissolved in DMSO (3.5 mL) and added dropwise to the reaction mixture. The mixture was allowed to warm to -15 °C, quenched with saturated aqueous $NaHCO_3$ (25 mL) and allowed to warm to ambient temperature. The reaction mixture was diluted with Et_2O (200 mL), washed with H_2O (50 mL), saturated aqueous $CuSO_4$ (3 x 50 mL), H_2O (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a colorless oil. The crude product could be purified using silica-gel chromatography (4:1, heptane-EtOAc) to afford **3.66** (605 mg, 86% yield) as a colorless oil, in practice, however, the crude product was used without further purification: R_f = 0.73 (heptane:EtOAc = 1:1); $[\alpha]^{23}_D$ = -30.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.9 Hz, 1H), 4.15-4.03 (m, 1H), 4.11 (d, *J* = 1.9 Hz, 1H), 3.65 (s, 3H), 2.51-2.29 (m, 2H), 1.78-1.53 (m, 3H), 1.52 (s, 3H), 1.39 (s, 6H), 1.34-1.13 (m, 1H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 200.2, 171.9, 110.0, 87.8, 83.5, 69.2, 51.5, 42.4, 31.6, 30.9, 27.9, 27.0, 25.7, 24.5, 17.9, -4.59, -4.95; IR (film) 2954, 2858, 1738, 1473, 1463, 1437, 1380, 1313, 1252, 1218, 1074, 1007, 837, 777; HRMS (ESP+) calc'd for $[M+Na]^+$) $C_{19}H_{36}O_6SiNa$ 411.2173, found 411.2173.

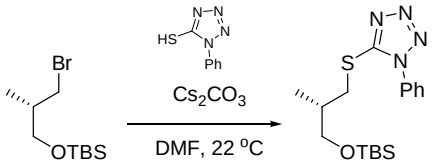
((*S*)-3-Bromo-2-methyl-propoxy)-*tert*-butyl-dimethyl-silane (3.67)



3.41 (94% yield) **3.67**

DMAP (969 mg, 8.1 mmol) was dissolved in CH_2Cl_2 (50 mL) and (*S*)-(–)-3-bromo-2-methyl-1-propanol (1.0 g, 6.5 mmol) was added followed by *tert*-butyl-chlorodimethylsilane (1.18 g, 7.8 mmol) while stirring at 22 °C. The mixture was stirred at 22 °C for an additional 12 h, diluted with Et_2O (100 mL), washed with H_2O (50 mL), saturated aqueous $CuSO_4$ (3 x 50 mL), H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless low-viscous oil. The crude product was purified using silica-gel chromatography (heptane) to afford **3.67** (1.64 g, 94% yield) as a colorless oil: R_f = 0.87 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = +11.8 (2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62-3.40 (m, 4H), 2.05-1.89 (m, 1H), 0.98 (d, *J* = 6.77 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 65.3, 38.1, 37.7, 25.9, 18.3, 15.5, -5.5; IR (film) 3050, 2955, 2930, 2858, 1472, 1387, 1361, 1337, 1258, 1231, 1143, 1101, 1021, 1006, 939, 837, 776, 668.

5-[(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propane-1-sulfanyl]-1-phenyl-1*H*-tetrazole (3.68)

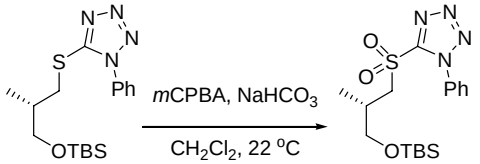


3.67 (95% yield) **3.68**

3.67 (500 mg, 1.87 mmol) was dissolved in DMF (10 mL). Cs_2CO_3 (1.22 g, 3.74 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (500 mg, 2.81 mmol) were added while stirring at 22 °C. The mixture was stirred at 22 °C for an additional 20 h, quenched with an aqueous solution of NaOH (10 mL, 5%), and extracted with heptane (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless oil. The crude product was purified using silica-gel chromatography (9:1, heptane-EtOAc) to afford **3.68** (647 mg, 95% yield) as a colorless oil: R_f = 0.31 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = -2.14 (2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.52 (m, 5H), 3.64 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.37 (dd, *J* = 12.8, 6.6 Hz, 1H); 3.52 (dd, *J* =

10.0, 5.7 Hz, 1H), 3.50 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.22-2.05 (m, 1H), 1.04 (d, *J* = 6.8, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.9, 133.7, 130.0, 129.7, 123.9, 66.3, 36.9, 35.5, 25.8, 18.2, 16.2, -5.5, -5.5; IR (film) 3070, 2956, 2857, 1598, 1501, 1471, 1386, 1316, 1250, 1146, 1088, 1015, 979, 939, 800, 760, 694, 667; HRMS (ESP+) calc'd for $C_{17}H_{28}N_4ONaSSi$ ($[M+Na]^+$) 387.1646, found 387.1659.

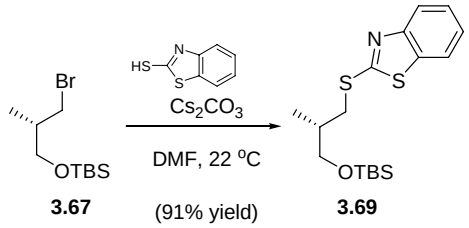
5-[(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propane-1-sulfonyl]-1-phenyl-1*H*-tetrazole (3.70)



3.68 (93% yield) **3.70**

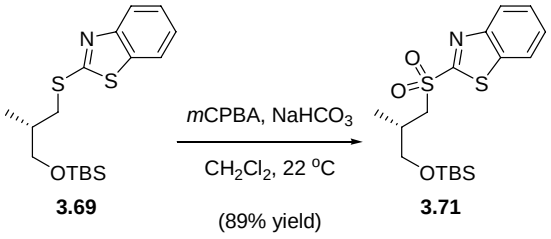
3.68 (640 mg, 1.76 mmol) was dissolved in CH_2Cl_2 (50 mL) and $NaHCO_3$ (740 mg, 8.8 mmol) was added while stirring at rt. *m*CPBA (760 mg, 4.4 mmol, ~70% pure) was dissolved in CH_2Cl_2 (50 mL) and added to the reaction mixture in one portion. The reaction mixture was stirred for an additional 10h, poured into a solution of saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous $Na_2S_2O_3$ (25 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to afford a colorless oil. The crude product was purified using silica-gel chromatography (9:1, heptane-EtOAc) to afford **3.70** (649 mg, 93% yield) as a colorless oil that crystallizes upon standing: mp 29-31 °C; R_f = 0.44 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = +3.59 (2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76-7.55 (m, 5H), 4.05 (dd, *J* = 14.6, 4.9 Hz, 1H), 3.72 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.55 (dd, *J* = 14.6, 7.7 Hz, 1H), 3.50 (dd, *J* = 10.0, 5.6 Hz, 1H), 2.57-2.37 (m, 1H), 1.16 (d, *J* = 6.9 Hz. 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.0, 133.1, 131.4, 129.7, 125.1, 66.1, 58.5, 31.2, 25.8, 18.2, 16.8, -5.5, -5.5; IR (KBr) 3078, 2929, 2858, 1499, 1473, 1328, 1260, 1153, 1100, 1027, 827, 777, 761, 687, 669, 631; HRMS (ESP+) calc'd for $C_{17}H_{28}N_4O_3NaSSi$ ($[M+Na]^+$) 419.1544, found 419.1552.

2-[(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propylsulfanyl]-benzothiazole (3.69)



3.67 (444 mg, 1.66 mmol) was dissolved in DMF (10 mL). Cs_2CO_3 (1.08 g, 3.31 mmol) and 2-mercaptobenzothiazole (333 mg, 1.99 mmol) were added while stirring at 22 °C. The suspension was stirred at 22 °C for an additional 14 h, quenched with an aqueous solution of NaOH (10 mL, 5%), and extracted with heptane (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless oil. The crude product was purified using silica-gel chromatography (9:1, heptane-EtOAc) to afford **3.69** (535 mg, 91% yield) as a colorless oil: R_f = 0.66 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = +5.05 (1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H), 7.75 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H), 7.44-7.36 (m, 1H), 7.28 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 3.66 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.55 (dd, *J* = 10.0, 5.9 Hz, 1H), 3.51 (dd, *J* = 12.9, 6.2, 1H), 3.23 (dd, *J* = 12.9, 7.1 Hz, 1H), 2.24-2.03 (m, 1H), 1.07 (d, 6.8 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.7, 153.3, 135.1, 125.9, 124.0, 121.4, 120.9, 66.4, 37.0, 36.0, 25.9, 18.3, 16.3, -5.4, -5.5; IR (film) 3050, 2956, 2928, 2857, 1463, 1429, 1387, 1361, 1309, 1251, 1096, 1018, 995, 939, 837, 776, 754, 726, 668; HRMS (ESP+) calc'd for $C_{17}H_{27}NONaS_2Si$ ($[M+Na]^+$) 376.1196, found 376.1183.

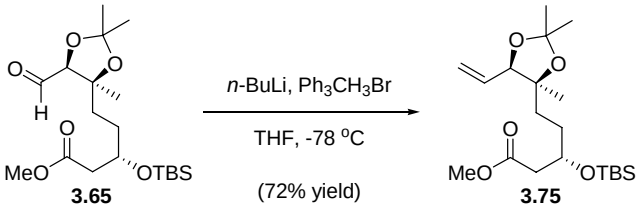
2-[(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propane-1-sulfonyl]-benzothiazole (3.71)



3.69 (300 mg, 0.85 mmol) was dissolved in CH_2Cl_2 (15 mL) and $NaHCO_3$ (357 mg, 4.25 mmol) was added while stirring at 22 °C. *m*CPBA (524 mg, 2.13 mmol, ~70% pure) was dissolved in CH_2Cl_2 (15 mL) and added to the reaction mixture in one portion. The reaction mixture was stirred for an additional 10h, poured into a solution of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). The organic layer was separated and the aqueous phase was extracted with

CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless oil. The crude product was purified using silica-gel chromatography (9:1, heptane-EtOAc) to afford **3.71** (291 mg, 89% yield) as a colorless oil: R_f = 0.40 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = +7.93 (1.3, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26-8.18 (m, 1H), 8.05-7.98 (m, 1H), 7.73-7.55 (m, 2H), 3.83 (dd, *J* = 14.5, 4.5 Hz, 1H), 3.64 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.43 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.29 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.51-2.30 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.82 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4, 152.7, 136.8, 127.9, 127.6, 125.5, 122.3, 66.2, 57.5, 31.5, 25.7, 18.1, 16.7, -5.5, -5.6; IR (film) 3050, 2959, 2930, 1557, 1471, 1394, 1326, 1252, 1149, 1025, 940, 836, 689, 667, 632; HRMS (ESP+) calc'd for $C_{17}H_{27}NO_3NaS_2Si$ ($[M+Na]^+$) 408.1095, found 408.1088.

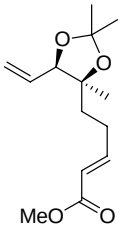
(3*S*,6*S*,7*R*)-7-*tert*-Butoxy-3-(*tert*-butyl-dimethyl-silanyloxy)-6-hydroxy-6-methyl-non-8-enoic acid methyl ester (3.75)



Triphenylphosphonium bromide (1.23 g, 2.04 mmol) was azeotroped with toluene (3 x 10 mL) and suspended in THF (50 mL). The suspension was cooled to -78 °C while stirring and *n*-BuLi (1.09 mL, 1.85 mmol, 1.7 M in cyclohexane) was added. The resulting bright yellow suspension was stirred at -78 °C for an additional 1 h. Crude **3.65** (~1.85 mmol) was azeotroped with benzene (3 x 10 mL), dissolved in THF (10 mL), and added dropwise to the reaction mixture while stirring. The reaction mixture was stirred at -78 °C for an additional 12 h. The mixture was allowed to warm to 22 °C and stirred for an additional 1 h, quenched with saturated aqueous NH_4Cl (25 mL), diluted with Et_2O (250 mL), washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified using silica-gel chromatography (9:1, heptane-EtOAc) to afford **3.75** (518 mg, 72% yield, from **3.65**) as a colorless oil: R_f = 0.18 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = -6.36 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H), 5.28 (ddd, *J* = 17.3, 1.7, 1.2 Hz, 1H), 5.16 (ddd, *J* = 10.5, 1.7, 1.2 Hz, 1H), 4.09 (dt, *J* = 6.9, 1.0, 1.0 Hz, 1H), 4.07-3.93 (m, 1H), 3.54 (s, 3H), 2.41-2.24 (m, 3H), 1.69-1.35 (m, 3H), 1.32 (s, 3H), 1.10 (s, 3H), 1.08-0.93 (m, 1H), 0.74 (s, 9H), -0.06 (s, 3H), -0.09 (s, 3H); ^{13}C

NMR (75.4 MHz, $CDCl_3$) δ 172.1, 132.50, 118.7, 107.6, 85.8, 82.2, 69.7, 51.4, 42.5, 31.1, 30.8, 28.2, 27.0, 25.7, 22.7, 17.9, -4.5, -5.0; IR (film) 3025, 2928, 2856, 1739, 1559, 1472, 1436, 1377, 1257, 1059, 924, 870, 838, 778; HRMS (ESP+) calc'd for $C_{20}H_{38}NO_5NaSi$ ($[M+Na]^+$) 409.2381, found 409.2392.

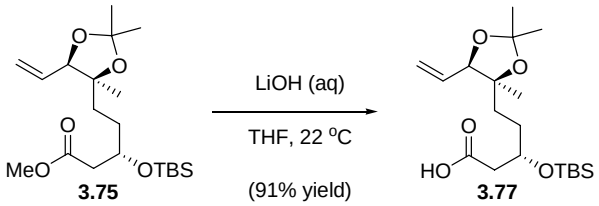
(*E*)-5-((4*S*,5*R*)-2,2,4-Trimethyl-5-vinyl-[1,3]dioxolan-4-yl)-pent-2-enoic acid methyl ester (3.76)



3.76

3.76 was isolated as a byproduct from the Wittig olefination of **3.65** as a colorless oil: R_f = 0.42 (heptane:EtOAc = 7:3); $[\alpha]^{23}_D$ = -28.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.90-5.73 (m, 1H), 5.83 (dt, *J* = 15.7, 1.6, 1H), 5.40 (ddd, *J* = 17.2, 1.6, 1.2 Hz, 1H), 5.29 (ddd, *J* = 10.5, 1.7, 1.0 Hz, 1H), 4.22 (dt, *J* = 6.9, 1.1 Hz, 1H), 3.72 (s, 3H), 2.48-2.32 (m, 1H), 2.32-2.14 (m, 1H), 1.78-1.62 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.36-1.26 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 67.1, 149.6, 132.3, 120.7, 119.0, 107.8, 85.8, 82.0, 51.4, 34.0, 28.3, 27.0, 26.2, 22.7; IR (film) 2985, 2936, 1726, 1658, 1436, 1378, 1327, 1265, 1218, 1194, 1105, 1056, 1024, 991, 911, 870, 799; HRMS (ESP+) calc'd for $C_{14}H_2O_4Na$ ($[M+Na]^+$) 277.1411, found 277.1409.

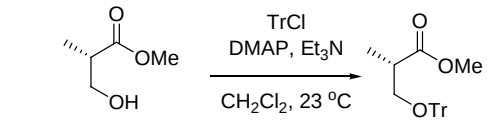
(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-((4*S*,5*R*)-2,2,4-trimethyl-5-vinyl-[1,3]dioxolan-4-yl)-pentanoic acid (3.77)



3.75 (100 mg, 0.259 mmol) was dissolved in THF (50 mL) and LiOH (25 mL, 0.3 M) was added. The solution was stirred at 22 °C for 20 h, diluted with EtOAc (100 mL), washed with NaH_2PO_4 (60 mL, 1.0 M in H_2O), brine (60 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a viscous oil. The crude product was purified using silica-gel chromatography (3:7 → 2:1, heptane-

EtOAc) to afford **3.77** (88 mg, 91%) as a colorless oil: R_f = 0.31 (heptane:EtOAc = 2:1); $[\alpha]^{23}_D$ = -25.9 (*c* 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.2, 10.5, 6.8 Hz, 1H), 5.46-5.32 (m, 1H), 5.28 (ddd, *J* = 10.5, 1.6, 1.1 Hz, 1H), 4.21 (dt, *J* = 6.9, 1.1, 1.1 Hz, 1H), 4.14-4.01 (m, 1H), 2.57-2.44 (m, 2H), 1.84-1.69 (m, 1H), 1.65-1.49 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H), 1.12 (dt, *J* = 14.6, 4.6, 4.6 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.9, 132.4, 118.8, 107.6, 85.8, 82.1, 69.7, 31.1, 30.8, 28.2, 27.0, 25.7, 22.7, 17.9, -4.6, -4.9; IR (film) 3092, 2932, 2857, 1711, 1473, 1377, 1251, 1219, 1251, 1219, 1058, 992, 927, 837, 776; HRMS (ESP+) calc'd for $C_{19}H_{36}O_5SiNa$ ($[M+Na]^+$) 395.2225, found 395.2235.

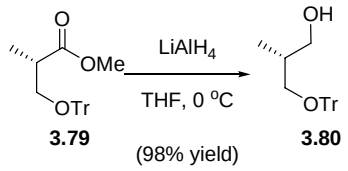
(2*S*)-Methyl-3-trityloxy-propionic acid methyl ester (3.79)



*(S)-Roche ester (**3.78**)* (96% yield) **3.79**

To a solution of trityl chloride (42.5 g, 152 mmol) in CH_2Cl_2 (250 mL) was added Et_3N (23.6 mL, 169 mmol), DMAP (2.06 g, 6.9 mmol), and (*S*)-Roche ester (**3.78**) (10.0 g 84.7 mmol). After stirring at 23 °C for 12 h the reaction was quenched with saturated aqueous NH_4Cl (100 mL), and diluted with CH_2Cl_2 (200 mL). The organic phase was washed with H_2O (3 x 200 mL), brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a pale yellow solid. The crude product was recrystallized from EtOH to afford **3.79** (29.3 g, 96% yield) as white needles: mp 90-91°C (EtOH), lit.[284] mp 84-85 °C (EtOH); R_f = 0.24 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = +17.7 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.40 (m, 6H), 7.35-7.19 (m, 9H), 3.71 (s, 3H), 3.31 (dd, *J* = 8.6, 7.1 Hz, 1H), 3.18 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.86-2.66 (m, 1H), 1.16 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.4, 143.9, 128.9, 127.8, 127.0, 86.3, 65.2, 51.6, 40.3, 13.9; IR (KBr) 3057, 3000, 2970, 2908, 2861, 1727, 1490, 1379, 1223, 1197, 1143, 1090, 990, 964, 902, 840, 771, 710, 697, 632. Spectral data are in accordance with literature values.[284]

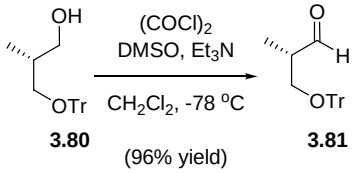
(2*R*)-Methyl-3-trityloxypropan-1-ol (3.80)



3.79 (98% yield) **3.80**

3.79 (25.0 g, 69.3 mmol) was dissolved in THF (500 mL) and cooled to 0 °C while stirring. $LiAlH_4$ (104 mL, 1.0 M solution in THF) was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for an additional 2 h and allowed to warm to 22 °C. After 2 h, the reaction was quenched carefully with H_2O (25 mL) followed by saturated aqueous Rochelle's salt (150 mL) The mixture was stirred for 12 h at 22 °C and diluted with Et_2O (500 mL). The aqueous layer was separated and extracted with Et_2O (2 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a colorless oil that crystallized upon standing. The crude solid was recrystallized from Et_2O and hexane to afford **3.80** (22.5 g, 98% yield) as a white solid: mp 69-71 °C (Et_2O, hexane), lit.[285] mp 74-76 °C (EtOAc, hexanes); R_f = 0.11 (heptane:EtOAc = 9:1); $[\alpha]^{23}_D$ = +29.1 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.40 (m, 6H), 7.37-7.18 (m, 9H), 3.70-3.51 (m, 2H), 3.24 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.03 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.33 (dd, *J* = 6.5, 5.1 Hz, 1H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 143.8, 128.5, 127.8, 127.0, 87.0, 67.6, 67.6, 35.9, 13.7; IR (KBr) 3313, 3057, 2959, 2909, 2868, 1596, 1488, 1448, 1215, 1160, 1073, 1033, 990, 775, 146, 706, 633. Spectral data are in accordance with literature values.[285]

(*S*)-2-Methyl-3-trityloxy-propionaldehyde (3.81)

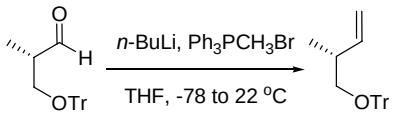


3.80 (96% yield) **3.81**

Oxalyl chloride (11.3 mL, 133 mmol) was dissolved in CH_2Cl_2 (250 mL) cooled to -78 °C. DMSO (23.6 mL, 333 mmol) was added dropwise keeping the internal temperature below -60 °C. The mixture was stirred at -78 °C for an additional 20 minutes. **3.80** (22.1 g, 66.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and added dropwise to the reaction mixture keeping the internal temperature below -70 °C. The mixture was stirred for an additional 45 minutes followed by addition of Et_3N (37 mL, 266 mmol). The reaction mixture was allowed to warm to 0 °C then quenched with saturated aqueous $NaHCO_3$ (100 mL). The organic phase was separated, washed with H_2O (100 mL),

saturated aqueous $CuSO_4$ (3 x 100 mL), H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a pale yellow solid. The crude product was recrystallized from hexane to afford **3.81** (21.1 g, 96% yield) as colorless needles with spectral: mp 91-93°C (hexanes); R_f = 0.60 (heptane:EtOAc = 1:1); $[\alpha]^{23}_D$ = +25.7 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.7 Hz, 1H), 7.49-7.40 (m, 6 H), 7.36-7.21 (m, 9H), 3.43-3.31 (m, 2H), 2.72-2.55 (m, 1H), 1.14 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 204.1, 143.6, 128.6, 127.8, 127.1, 86.6, 63.6, 47.0, 10.8; IR(KBr) 3085, 3059, 2979, 2867, 2830, 2740, 1720, 1596, 1488, 1449, 1400, 1219, 1154, 1122, 1092, 1076, 1047, 778, 768, 711, 698, 632. Spectral data are in accordance with literature values.[286]

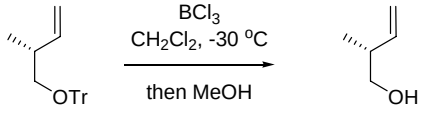
(3*S*)-Methyl-4-trityloxybut-1-en (3.73)



3.81 (89% yield) **3.73**

Triphenylphosphonium bromide (32.5 g, 90.9 mmol) was azeotroped with toluene (3 x 50 mL) and suspended in THF (500 mL). The suspension was cooled to -78 °C while stirring and *n*-BuLi (47.2 mL, 86.3 mmol, 1.83 M in cyclohexane) was added dropwise. The resulting bright yellow suspension was stirred at -78 °C for an additional 1 h. **3.81** (15.0 g, 45 mmol) was dissolved in THF (50 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at -78 °C, allowed to warm to room 22 °C. After an additional 12 h stirring at 22 °C the reaction was quenched with MeI (6.2 mL, 100 mmol), stirred for 2 h at 22 °C, diluted with Et_2O (500 mL), washed with H_2O (3 x 200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a pale yellow oil. The crude product was purified using silica-gel chromatography (19:1, heptane-EtOAc) to afford **3.71** (13.2 g, 89%) as a colorless viscous oil: R_f = 0.63 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$ = -1.53 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.10 (m, 15H), 5.82 (ddd, *J* = 17.3, 10.4, 7.0 1H), 5.12-4.96 (m, 2H), 3.01 (dd, *J* = 8.6, 6.6 Hz, 1H), 2.93 (dd, *J* = 8.6, 6.6 Hz, 1H), 2.58-2.40 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H);^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.3, 141.7, 128.7, 127.7, 126.8, 113.8, 86.1, 68.0, 38.3, 16.8; IR (film) 3061, 3034, 2963, 2911, 2867, 1639, 1595, 1489, 1447, 1418, 1382, 1365, 1215, 1153, 1030, 994, 924, 898, 775, 741, 697; HRMS (ESP+) calc'd for $C_{24}H_{24}ONa$ ([M+Na^+]) 351.1720, found 353.1721.

(*R*)-2-Methyl-but-3-en-1-ol (3.82)

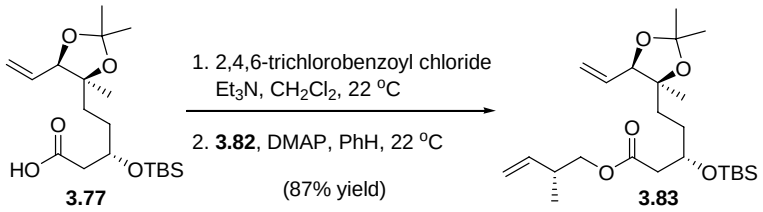


3.73 **3.82**

clean reaction by TLC
attained as a solution in CH_2Cl_2

3.73 (2.0 g, 6.1 mmol) was dissolved in CH_2Cl_2 (10 mL) and the resulting clear solution was cooled to -30 °C while stirring. BCl_3 (3.67 mL, 3.67 mmol, 1.0 M in CH_2Cl_2) was added dropwise. The mixture became bright yellow instantaneously. The mixture was stirred for an additional 30 min at -30 °C and was subsequently quenched with MeOH (1.0 mL) and poured into saturated aqueous $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (1 x 10 mL). The combined organic phases were washed with brine (25 mL), and dried over $MgSO_4$ to afford a solution of **3.82** in CH_2Cl_2 (~0.3M) along with TrOMe (~0.3 M). This solution was used for the subsequent esterification reaction.

(S)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-((4*S*,5*R*)-2,2,4-trimethyl-5-vinyl-[1,3]dioxolan-4-yl)-pentanoic acid (*R*)-2-methyl-but-3-enyl ester (3.83)

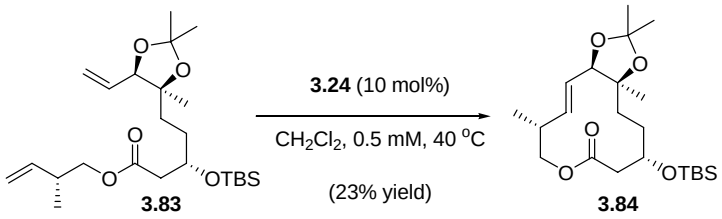


3.77 **3.83**

3.77 (50 mg, 0.134 mmol) was azeotroped with benzene (3 x 5 mL) and dissolved in CH_2Cl_2 (2.5 mL). Triethylamine (296 µL, 2.13 mmol) was added in one portion followed by 2,4,6-trichlorobenzoyl chloride (167 µL, 1.07 mmol). The resulting solution was allowed to stir for an additional 30 minutes at 22 °C, then the reaction mixture was taken up into a syringe, and added to a solution of DMAP (211 mg, 1.73 mmol) and **3.82** (~0.67 mmol, as ~0.3 M solution in CH_2Cl_2) in benzene (25 mL). The resulting cloudy yellow suspension was stirred for 20 h at 22 °C. Saturated aqueous $NaHCO_3$ (25 mL) was added to the reaction mixture and the resulting biphasic mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo* to afford a pale yellow residue. The crude product was purified using silica-gel chromatography (9:1 → 4:1, heptane-EtOAc) to afford **3.83** (52 mg, 87% yield): R_f = 0.59 (heptane:EtOAc = 4:1); $[\alpha]^{23}_D$

= - 3.4 (*c* 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.3, 10.4, 6.9 Hz, 1H), 5.74 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1H), 5.48-5.33 (m, 1H), 5.28 (ddd, *J* = 10.4, 1.6, 1.0 Hz, 1H), 5.07 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.06-5.00 (m, 1H), 4.20 (dt, *J* = 6.9, 1.0 Hz, 1H), 4.16-4.05 (m, 1H), 3.99 (dd, *J* = 10.7, 6.8 Hz, 1H), 3.89 (dd, *J* = 10.7, 6.7 Hz, 1H), 2.72-2.17 (m, 3H), 1.77-1.47 (m, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.21 (s, 3H), 1.17-1.06 (m, 1H), 1.04 (d, *J* = 6.83 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.7, 140.0, 132.5, 118.8, 114.9, 107.6, 85.9, 82.2, 69.6, 68.3, 42.7, 36.8, 31.1, 30.9, 28.2, 27.1, 25.8, 22.7, 17.9, 16.4, -4.5, -4.9; IR (film) 3058, 2932, 2877, 2847, 1735, 1473, 1377, 1351, 1217, 1058, 1000, 919, 887, 776; HRMS (ESP+) calc'd for $C_{24}H_{44}O_5SiNa$ ($[M+Na]^+$) 463.2851, found 463.2861.

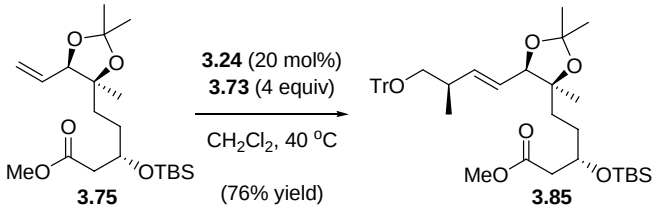
(*E*)-(3a*R*,6*R*,11*S*,13a*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,2,6,13a-tetramethyl-3a,6,7,10,11 ,12,13,13a-octahydro-1,3,8-trioxa-cyclopentacyclododecen-9-one (3.84)



3.83 **3.84**

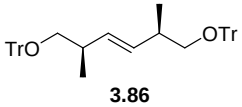
3.83 (50 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (227 mL) and deoxygenated via argon purge and sonication. Hoveyda-Grubbs' 2nd generation catalyst (**3.24**) (6.9 mg, 0.011 mmol) was added and the resulting clear green solution was heated to reflux while stirring. After 20 h stirring TLC revealed full conversion of the starting material and the mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The crude product was purified using silica-gel chromatography (19:1, heptane-EtOAc) to afford **3.84** (10.4 mg, 23% yield) as a colorless oil. For characterization data cf. the macrolactonization approach.

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-[(4*S*,5*R*)-2,2,4-trimethyl-5-((*E*)-(*R*)-3-methyl-4-trityl-oxy-but-1-enyl)-[1,3]dioxolan-4-yl]-pentanoic acid methyl ester (3.85)



3.75 (313 mg, 0.81 mmol) and **3.73** (533 mg, 1.62 mmol) were dissolved in CH_2Cl_2 (25 mL) and deoxygenated via argon purge and sonication (5 min). Hoveyda-Grubbs' 2nd generation catalyst (**3.24**) (38 mg, 0.081 mmol) was added and the mixture was deoxygenated via argon purge and sonication (5 min). The mixture was heated to reflux and stirred for 20 h, then additional **3.73** (533 mg, 1.62 mmol) and **3.24** (19 mg, 0.041 mmol) were added. After an additional 18 h of stirring at reflux, a final portion of **3.24** (19 mg, 0.041 mg) was added. The resulting green solution was stirred 18 h at reflux. The solvent was then removed *in vacuo*, and the residue was purified using silica-gel chromatography (19:1 → 9:1, heptane-EtOAc) to afford **3.85** (422 mg, 76% yield) as a colorless oil: R_f = 0.42 (heptane:EtOAc = 1:1); $[\alpha]^{23}_D$ = -15.9 (*c* 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.20 (m, 15 H), 5.81 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.45 (ddd, *J* = 15.4, 7.9, 1.1 Hz, 1H), 4.14 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.15-4.06 (m, 1H), 3.66 (s, 3H), 3.03 (dd, *J* = 8.7, 6.5 Hz, 1H), 2.94 (dd, *J* = 8.7, 6.6 Hz, 1H), 2.51-2.34 (m, 3H), 1.75-1.53 (m, 3H) 1.42 (s, 3H), 1.36 (s, 3H), 1.17 (s, 3H), 1.07-0.91 (m, 1H),1.06 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.1, 144.2, 139.5, 128.7, 127.7, 126.9, 123.6, 107.3, 86.2, 86.0, 82.2, 69.8, 67.9, 51.5, 42.7, 37.4, 31.1, 31.0, 28.3, 27.1, 25.7, 22.5, 17.9, 17.0, -4.4, -4.9; IR (film)3050, 3030, 2954, 2929, 2851, 1741, 1449, 1376, 1251, 1217, 1075, 1085, 974, 836, 775, 707; HRMS (ESP+) calc'd for $C_{42}H_{58}O_6NaSi$ ([M+Na]$^+$) 709.3895, found 709.3921.

((*E*,2*R*,5*R*)-2-Methyl-5-((trityloxy)methyl)hex-3-enyloxy)triphenylmethane (3.86)

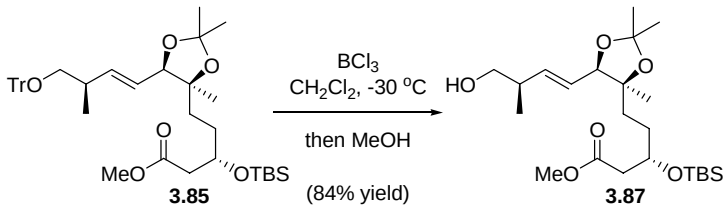


3.86

3.86 was isolated as a byproduct from the CM of **3.75** as a white powder: R_f = 0.43 (heptane:EtOAc = 9:1); $[\alpha]^{22}_D$ = -8.4 (*c* 2.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.42 (m, 12H), 7.36-7.17 (m, 18H), 5.43 (dd, *J* = 4.1, 1.9 Hz, 2H), 3.03 (dd, *J* = 8.6, 6.4 Hz, 2H), 2.91 (dd, *J* = 8.6, 7.0 Hz,

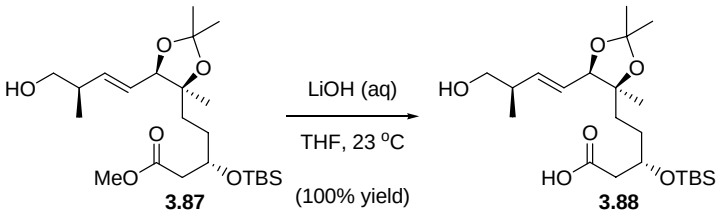
2H), 2.55-2.36 (m, 2H), 1.07 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.4, 132.7, 128.7, 127.6, 126.7, 86.0, 68.2, 37.3, 17.4; IR (film) 3058, 3022, 2962, 2908, 2882, 2867, 1491, 1448, 1215, 1181, 1151, 1074, 1030, 1074, 1030, 1003, 983, 897, 763, 702, 633; HRMS (ESP+) calc'd for $C_{46}H_{44}O_3Na$ ([M+Na]$^+$) 651.3234, found 651.3216.

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-[(4*S*,5*R*)-5-((*E*)-(*R*)-4-hydroxy-3-methyl-but-1-enyl)-2,2,4-trimethyl-[1,3]dioxolan-4-yl]-pentanoic acid methyl ester (3.87)



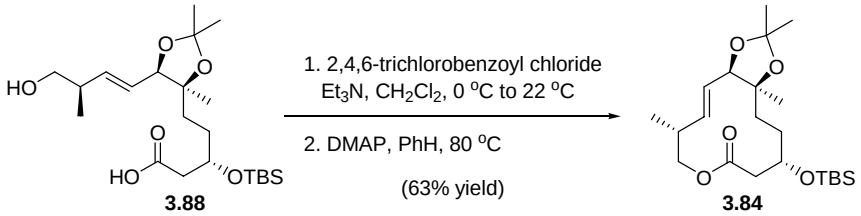
3.85 (146 mg, 0.213 mmol) was dissolved in CH_2Cl_2 (10 mL) and the resulting clear solution was cooled to -30 °C while stirring. BCl_3 (128 µL, 0.128 mmol, 1.0 M in CH_2Cl_2) was added dropwise. The mixture became bright yellow instantaneously. The mixture was stirred for an additional 30 min at -30 °C and was subsequently quenched with MeOH (3.0 mL) and poured into saturated aqueous $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford a colorless sticky oil. The crude product was purified using silica-gel chromatography (4:1 → 2:1, heptane-EtOAc) to afford **3.87** (80.4 mg 84% yield) as a colorless oil: R_f = 0.44 (heptane:EtOAc = 3:7); $[\alpha]^{23}_D$ = +2.7 (*c* 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 15.6, 7.3, 0.8 Hz, 1H), 5.53 (ddd, *J* = 15.6, 7.4, 1.1 Hz, 1H), 4.19 (dd, *J* = 7.4, 0.8 Hz, 1H), 4.18-4.04 (m, 1H), 3.65 (s, 3H), 3.60-3.38 (m, 2H), 2.50-2.30 (m, 1H), 2.48 (dd, *J* = 14.6, 7.1 Hz, 1H), 2.39 (dd, *J* = 14.6, 5.7 Hz, 1H), 1.78-1.49 (m, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.28-1.10 (m, 1H), 1.19 (s, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 172.2, 137.6, 125.2, 107.4, 85.5, 82.2, 69.6, 67.2, 51.5, 42.6, 39.4, 31.0, 30.7, 28.2, 27.1, 25.7, 22.7, 17.9, 16.1, -4.5, -4.9; IR (film) 3450, 2930, 1732, 1443, 1405, 1220, 1105, 830, 777, 705; HRMS (ESP+) calc'd for $C_{23}H_{44}O_6SiNa$ ([M+Na]$^+$) 469.2799, found 469.2785.

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-[(4*S*,5*R*)-5-((*E*)-(*R*)-4-hydroxy-3-methyl-but-1-enyl)-2,2,4-trimethyl-[1,3]dioxolan-4-yl]-pentanoic acid (3.88)



3.87 (59 mg, 0.132 mmol) was dissolved in THF (50 mL) and LiOH (25 mL, 0.3 M) was added. The solution was stirred at 23 °C for 13 h, diluted with EtOAc (100 mL), washed with NaH_2PO_4 (60 mL, 1.0 M in H_2O), brine (60 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford a viscous oil. The crude product was purified using silica-gel chromatography (3:7 → 0:1, heptane-EtOAc) to EtOAc) to afford **3.88** 57 mg (100%) as a colorless oil: R_f = 0.32 (heptane:EtOAc = 3:7); $[\alpha]^{23}_D$ = -12.8 (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 15.6, 7.30, 0.6 Hz, 1H), 5.51 (ddd, *J* = 15.6, 7.4, 1.0 Hz, 1H), 5.40 (br s, 2H), 4.18 (dd, *J* = 7.3, 1.0 Hz, 1H), 4.13-4.01 (m, 1H), 3.58-3.41 (m, 2H), 2.57-2.33 (m, 3H), 1.78-1.49 (m, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.28-1.11 (m, 1H), 1.19 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.3, 137.7, 125.0, 107.4, 85.4, 82.2, 69.7, 67.0, 42.2, 39.2, 31.3, 31.1, 28.3, 27.0, 25.7, 22.7, 17.9, 16.1, -4.6, -5.0; IR (film) 3395, 2954, 2930, 2857, 1713, 1472, 1463, 1377, 1256, 1218, 1192, 1094, 1035, 974, 922, 837, 812, 776, 735; HRMS (ESP+) calc'd for $C_{22}H_{42}O_6SiNa$ ($[M+Na]^+$) 453.2643, found 453.2622.

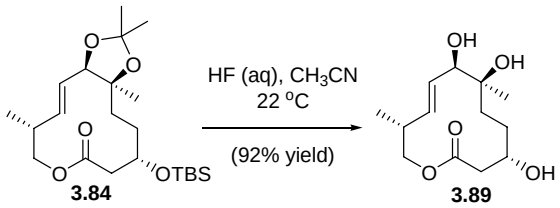
(*E*)-(3a*R*,6*R*,11*S*,13a*S*)-11-(*tert*-Butyl-dimethyl-silanyloxy)-2,2,6,13a-tetramethyl-3a,6,7,10,11,-12,13,13a-octahydro-1,3,8-trioxa-cyclopentacyclododecen-9-one (3.84)



3.88 (36.4 mg, 0.085 mmol) was azeotroped with benzene (3 x 5 mL) and dissolved in CH_2Cl_2 (3.0 mL). Triethylamine (188μL, 1.35 mmol) was added in one portion followed by 2,4,6-trichlorobenzoyl chloride (106 μL, 0.68 mmol). The resulting solution was allowed to stir for an additional 30 minutes at room 22 °C and then the reaction mixture was diluted with benzene (10

mL), taken up into a syringe, and added dropwise over 1h by use of a syringe pump to a refluxing solution of DMAP (134 mg, 1.10 mmol) in benzene (225 mL). The resulting cloudy yellow suspension was stirred for an additional 30 minutes at reflux and allowed to cool to ambient temperature. Saturated aqueous $NaHCO_3$ (100 mL) was added to the reaction mixture and the resulting biphasic mixture was stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo* to afford a pale yellow residue. The crude product was purified using silica-gel chromatography (19:1, heptane-EtOAc) to afford **3.84** (21.1 mg, 63% yield) as a colorless oil: R_f = 0.38 (heptane:EtOAc = 9:1); $[\alpha]^{23}_D$ = -5.7 (*c* 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (dd, *J* = 15.5, 7.7 Hz, 1H), 5.46 (dd, *J* = 15.5, 8.0 Hz, 1H), 4.20 (d, *J* = 7.7 Hz, 1H), 4.05-3.88 (m, 3H), 2.80-2.60 (m, 1H), 2.55 (dd, *J* = 14.2, 4.3 Hz, 1H), 2.32 (dd, *J* = 14.2, 10.7 Hz, 1H), 1.75 (ddd, 13.3, 11.6, 7.7 Hz, 1H), 1.64-1.48 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.33 (ddd, *J* = 10.9, 5.4, 2.6 Hz, 1H), 1.29 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.5, 136.1, 129.2, 107.8, 84.6, 83.3, 71.2, 67.3, 43.7, 36.9, 34.7, 31.9, 28.9, 27.2, 25.7, 25.3, 18.0, 16.0, -4.5, -4.6; IR (film) 3026, 2964, 2932, 2862, 1733, 1472, 1451, 1374, 1267, 1190, 1103, 1082, 1046, 1005, 974, 923, 887, 837, 774; HRMS (ESP+) calc'd for ($[M+Na]^+$) 435.2537, found 435.2524.

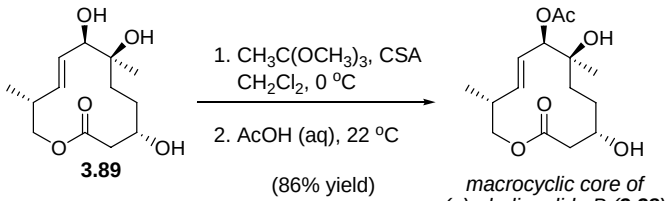
(*E*)-(4*S*,7*S*,8*R*,11*R*)-4,7,8-Trihydroxy-7,11-dimethyl-oxacyclododec-9-en-2-one (3.89)



3.84 (19.6 mg, 48 μmol) was dissolved in MeCN (10 mL) and HF (0.5 mL, 40%) was added while stirring at 22 °C. The solution was stirred at 22 °C for 3 h and poured into saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc (25 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (5 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford a white solid. The crude product was purified using silica-gel chromatography (EtOAc) to afford **3.89** (11.3 mg, 92% yield) as a white powder: R_f = 0.20 (EtOAc); $[\alpha]^{23}_D$ = -9.12 (*c* 0.19, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 5.69 (dd, *J* = 15.2, 9.5 Hz, 1H), 5.34 (dd, *J* = 15.2, 9.7 Hz, 1H), 4.40 (t, *J* = 10.8 Hz, 1H), 3.85-3.47 (m, 1H), 3.73

(dd, *J* = 10.8, 4.9 Hz, 1H), 3.71 (d, *J* = 9.6 Hz, 1H), 2.69-2.55 (m, 1H), 2.54-2.52 (m, 2H), 1.64-1.43 (m, 2H), 1.50-1.13 (m, 2H), 1.26 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 172.7, 137.6, 131.8 78.2, 74.5, 70.5, 67.8, 40.0, 39.7, 37.2, 30.2, 24.7, 16.2; IR (film) 3344, 293, 2841, 1720, 1651, 1564, 1501, 1462, 1400, 1350, 1092, 917, 880, 775; HRMS (ESP+) calc'd for $C_{13}H_{22}O_5Na$ ($[M+Na]^+$) 281.1359, found 281.1351.

Acetic acid (*E*)-(3*R*,6*R*,7*S*,10*S*)-7,10-dihydroxy-3,7-dimethyl-12-oxo-oxacyclododec-4-en-6-yl ester (3.38)



3.89 (9.4 mg, 36 μmol) was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to 0 °C while stirring. Trimethyl orthoacetate (46 μL, 364 μmol) was added in one portion followed by CSA (one grain). The mixture was stirred at 0 °C for an additional 1.5 h and AcOH (5 mL, 80% in water) was added in one portion. The reaction mixture was allowed to warm to 22 °C and stirred for an additional 1.5 h. The solvent was removed *in vacuo* and the crude mixture was azeotroped with toluene (3 x 5 mL) to afford a white powder. The crude product was purified using silica-gel chromatography (3:7, heptane-EtOAc) to afford **3.38** (9.4 mg, 86%) as a white powder. X-ray quality crystals were obtained by recrystallization from diisopropylether and methanol: R_f = 0.16 (heptane:EtOAc = 3:7); $[\alpha]^{23}_D$ = -45.1 (*c* 0.059 , $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (dd, *J* = 15.2, 9.30 Hz, 1H), 5.53 (dd, *J* = 15.2, 9.6 Hz, 1H), 5.07 (d, *J* = 9.3 Hz, 1H), 4.69 (dd, *J* =11.8, 10.9 Hz, 1H), 3.83-3.68 (m, 1H), 3.58 (dd, *J* = 10.9, 4.9 Hz, 1H), 2.66 (dd, *J* = 15.4, 3.7, 1H), 2.61-2.46 (m, 1H), 2.55 (dd, *J* = 15.4, 3.1 Hz, 1H), 2.09 (s, 3H), 1.77-1.56 (m, 1H), 1.56-1.44 (m, 1H), 1.45-1.23 (m, 2H), 1.20 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.6, 169.6, 140.4, 125.9, 78.7, 73.3, 69.1, 66.1, 39.1, 38.0, 35.1, 29.6, 24.7, 21.3, 15.6; IR (film) 3453, 3000, 2947, 2885, 1733, 1707, 1463, 1427, 1375, 1256, 1173, 1137, 1101, 1080, 1054, 1023, 992, 920, 899, 800, 743, 668, 666; HRMS (ESP+) calc'd for $C_{15}H_{24}O_6Na$ ($[M+Na]^+$) 323.1465, found 323.1450.

4 Ruthenium- and Iridium-Catalyzed C-C Bond Formation

A pivotal challenge in synthetic organic chemistry is the efficient construction of C-C bonds allowing for the rapid build-up of molecular complexity. The last three to four decades have seen the appearance of several highly efficient transition metal catalyzed C-C bond forming protocols offering great control in terms of chemo-, diastereo-, and enantioselectivity. Prominent among these processes are the olefin metathesis reaction[121] (cf. chapter 2.4) and the palladium-catalyzed coupling reactions.[287,288] When evaluating these processes from an atom economical perspective the olefin metathesis clearly stands out as a superior transformation, since ethylene is the only formed byproduct,[a] whereas palladium-catalyzed cross-coupling reactions produce large amounts of inorganic salts often with relatively high molecular weight. The term atom economy was introduced in 1991 by Professor Barry M. Trost from Stanford University (Figure 4.1).[289-292] This term was meant to serve as a guiding principle for evaluating the efficiency of specific chemical processes and moreover highlight the limitations associated with the conventional yield and selectivity founded assessment of synthetic efficiency.

$$\text{reaction yield} = \frac{\text{quantity of product}}{\text{theoretical quantity of product}} \times 100\%$$

$$\text{atom economy} = \frac{M_w \text{ of desired product}}{M_w \text{ of all products}} \times 100\%$$

Figure 4.1 Traditional reaction yield vs. atom economy.

The reaction yield is only concerned with the quantity of the desired product that is isolated relative to the theoretical quantity of the product. In contrast atom economy takes all used reagents and unwanted products into account along with the desired product. A corollary of the atom economy concept is that if maximum incorporation of reagents into the product cannot be achieved, then ideally the amount of side product (waste) should be minute and environmentally innocuous. As is evident from the cross coupling reactions, which are some of the true work horses in organic synthesis, there is still vast room for improvement in striving toward environmentally benign chemical transformations. Recently, Noyori stated the following goal for future synthetic chemists: “Ideally, we should aim at synthesizing target compounds with 100% yield and 100% selectivity and

[a] In the case of ring-opening metathesis polymerization no byproduct is formed i.e. the atom economy is 100%.

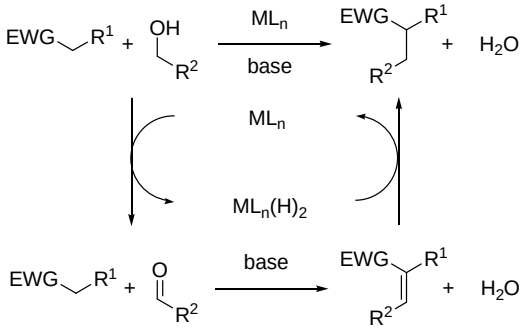
avoid the production of waste. This process must be economical, safe, resource-efficient, energy-efficient and environmentally benign."[293]

A recent approach to construct C-C bonds in a catalytic manner relies on a transition metal catalyzed hydrogen autotransfer process to couple alcohols and various carbon nucleophiles producing water as the only byproduct. Hereby providing a "greener" alternative to the traditional coupling of enolate derivatives and alkyl halides/pseudohalides.[294-296]

4.1 The Transition Metal-Catalyzed Hydrogen Autotransfer Process

4.1.1 Background

A traditional means to construct C-C bonds in organic synthesis is based on the coupling of enolate derivatives with alkyl halides. From an atom economical and environmental perspective this approach suffers from several disadvantages, such as the required use of stoichiometric amounts of strong base and generation of large amounts of waste resulting from the halide leaving group. An emerging alternative is the hydrogen autotransfer process. This process, allowing for alkylation of diverse nucleophiles *e.g.* ketones, nitriles and activated methylene compounds using alcohols, was demonstrated by Guerbert[297] already in 1908. However, this process had received sparse attention until recent developments by particularly Grigg,[298] Cho,[299,300] Yus,[301,302] and Williams.[303,304]

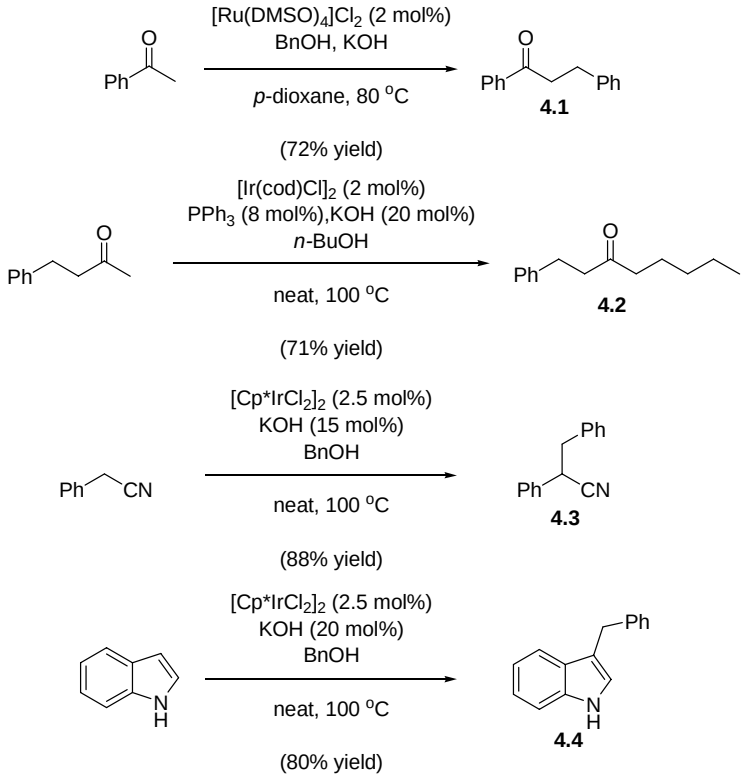


Scheme 4.1 Hydrogen autotransfer process.

Common features for these hydrogen autotransfer processes are the involvement of three fundamental steps: transition metal catalyzed alcohol dehydrogenation affording an aldehyde/ketone, which undergoes condensation or olefination to furnish an unsaturated product, which is ultimately hydrogenated delivering the saturated product (Scheme 4.1). Overall this process

changes the usual nucleophilic reactivity of alcohols by *in situ* generation of a highly electrophilic aldehyde poised to undergo reaction with an appropriate nucleophile furnishing the desired alkylated product with water as the only byproduct.

Recently, several iridium and ruthenium based protocols for the alkylation of *e.g.* ketones,[300,301,305-307] barbiturates,[308] and certain nitriles[309-312] have been disclosed (representative examples are depicted in Scheme 4.2). Yus[302] disclosed the facile α-alkylation of ketones utilizing $[Ru(DMSO)_4]Cl_2$ as catalyst and achieved the formation of **4.1** in 72% yield. The iridium based catalyst system consisting of $[Ir(cod)Cl]_2$ and PPh_3 was also found to be an efficient catalyst for the alkylation of ketones with primary alcohols.[305] Notably, this methodology proceeded with excellent regioselectivity affording **4.2** in high yield. Grigg and co-workers[310,313] have reported the iridium-catalyzed alkylation of arylacetonitriles furnishing **4.3** and additionally utilized indoles as nucleophiles in alkylation reactions with alcohols to provide **4.4**.



Scheme 4.2 Representative alkylation protocols with alcohols.

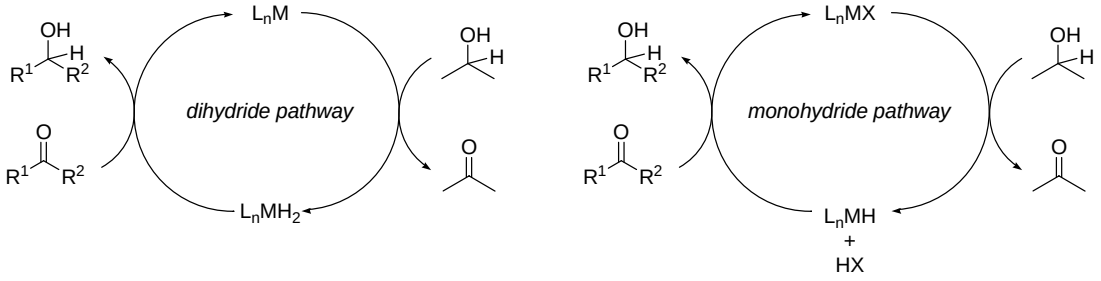
In recent years a range of heterogeneous catalyst have also been shown to facilitate related alkylation processes, including polymer supported palladium,[314] palladium nanoparticles in

aluminium hydroxide,[306] ruthenium-grafted hydrotalcite,[309] alumina-supported silver particles,[315] and nickel nanoparticles.[307] Additionally, this methodology has found widespread application in the construction of various heterocycles,[316-321] alkylation of amines,[322-326] carbamates/amides[327], and sulfonamides.[328] Considering the aforementioned examples, the hydrogen autotransfer process have obviously emerged as an atom efficient and "green" protocol for the alkylation of various nucleophiles utilizing primary alcohols. However, future progress to provide more active catalysts to make this process operational at ambient temperatures, encompass secondary alcohols, and allow for asymmetric alkylations is necessary to provide a powerful synthetic tool.

4.1.2 Mechanistic Considerations

The mechanistic scenario of the transfer hydrogenation of carbonyl compounds with alcohols and of the transition metal catalyzed reduction of α,β-unsaturated carbonyl species have been subject to intense investigations.[329] In contrast a combined mechanistic understanding of the hydrogen autotransfer process utilizing alcohols to alkylate *e.g.* ketones has hitherto not attracted much attention and mechanisms proposed by Cho,[300] Yus,[302] and Williams[330] are mostly based on speculation providing cycles similar to the one depicted in scheme 4.1.

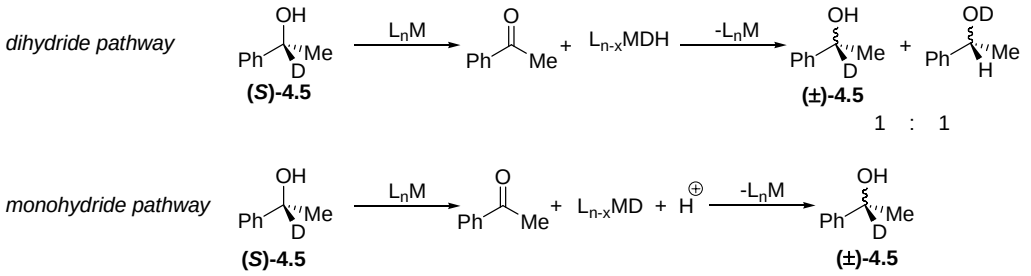
For transition metals it is widely accepted that hydrogen transfer reactions can occur via two main pathways involving either a monohydride or a dihydride metal intermediate (Scheme 4.3).[329]



Scheme 4.3 Dihydride and monohydride pathways.

The dihydride route involves a formal oxidative addition with regard to the metal center followed by a reductive elimination. Conversely, the monohydride pathway contains no formal change in the oxidation state of the metal center. A general feature for catalysts operating through the dihydride mechanism is that the C-H and O-H loose their "identity" when they are transferred to the acceptor. This can be ascribed to the fact that the two hydrogens become equivalent after being transferred to

the metal center. In the monohydride case the C-H hydrogen from the donor ends up as C-H in the product. The reason for this observation is that only the C-H hydrogen forms the hydride on the metal, thus being transferred to the carbonyl carbon of the acceptor.[331] Bäckvall has designed a clever experiment to determine whether the dihydride or the monohydride pathway is operational. That is racemization of α-deuterated (*S*)-phenylethanol (**(*S*)-4.5**) (Scheme 4.4). If the dihydride mechanism is occurring the deuterium will be scrambled between carbon and oxygen, whereas the monohydride pathway will exclusively incorporate deuterium at carbon.[332]



Scheme 4.4 Mono vs. dihydride mechanism.

In general the rhodium- and iridium-catalyzed hydrogen transfer reactions proceeded via the monohydride mechanism, exhibiting little dependence on the ancillary ligand. The outcome on the ruthenium-catalyzed racemizations varied depending on the catalyst precursor employed. For instance The reaction utilizing [$RuCl_2PPh_3$] was shown to proceed via the dihydride pathway (37% **(±)-4.5**), whereas Shvo's catalyst (cf. Table 4.1)[333] operated through the monohydride mechanism (95% **(±)-4.5**).[332]

4.2 Alkylation of Oxindoles

4.2.1 Background and Significance

The oxindoles, specifically those containing C(3) functionalization represent a common and important motif in numerous natural products[334-339] and biologically active molecules.[340-344] An important example is the tyrosine kinase inhibitor sunitinib (**4.6**), which is marketed by Pfizer Inc. as an antitumor agent (Figure 4.2a). Recently He and co-workers[340] disclosed the synthesis and biological evaluation of spirocyclopropane **4.7** exhibiting significant inhibition of HIV-1 non-nucleoside reverse transcriptase (EC_{50} = 15 nM, for comparison nervirapine, which is in clinical use has EC_{50} = 50 nM). In 2008 researchers from EGIS pharmaceuticals identified **4.8** as a 5-HT7

receptor antagonist. Hitherto the functional significance of the 5-HT7 receptor is largely unknown, however, this receptor has been associated with a variety of CNS functions and disorders *e.g.* schizophrenia[345] and depression.[346,347]

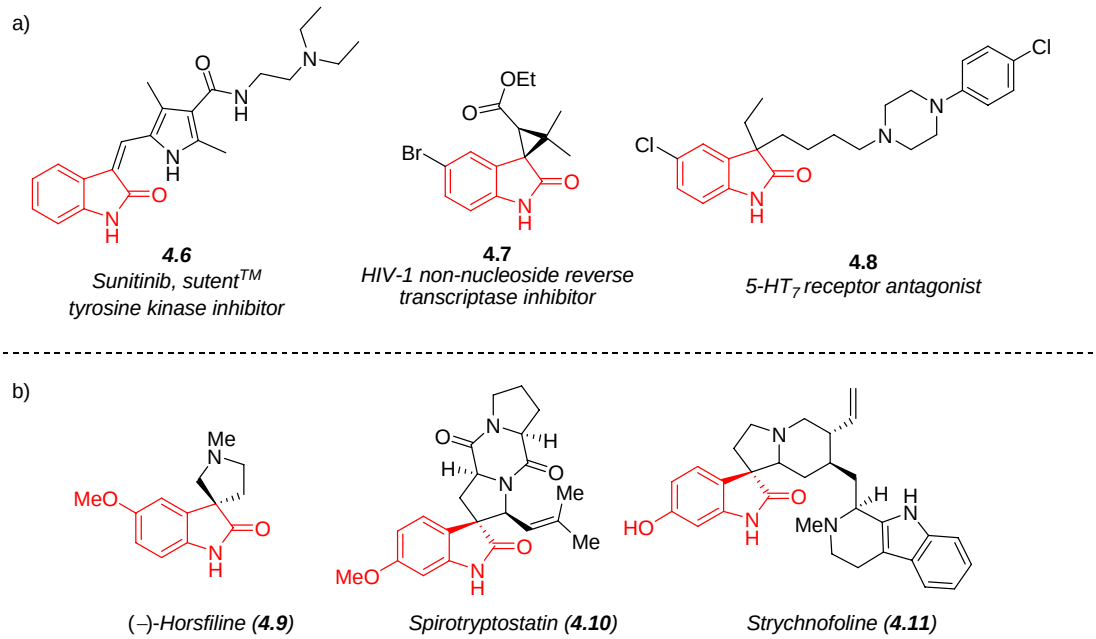
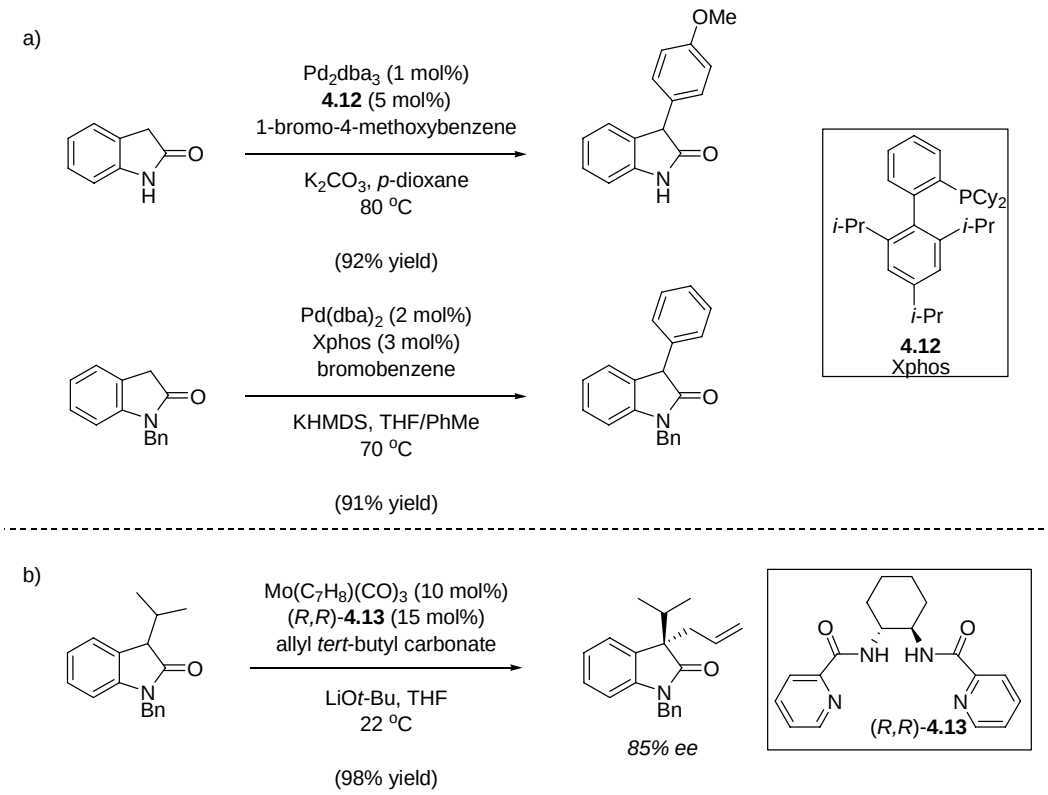


Figure 4.2 Representative biologically active 3-substituted oxindoles.

The 3,3'-pyrrolidinyl-spirooxindole motif holds a prominent position among oxindole based natural products (Figure 4.2b).[336] (–)-Horsfiline (**4.9**) was disclosed in 1991[348], spirotryptostatin (**4.10**) was isolated from the fermentation broth of Aspergillus fumigatus,[349] and strychnofoline (**4.11**) from the leaves of Strychnos usambarensis.[350] Both spirotryptostatin (**4.10**) and strychnofoline (**4.11**) have shown potential as anticancer agents by virtue of their ability to inhibit mitosis in a number of cell lines.[336]

In recent years several excellent methods to arylate and allylate the C(3) position of oxindole have appeared. Willis[351] and later Buchwald[352] have efficiently arylated the C(3) position of oxindoles employing palladium in combination with the bulky electron rich phosphine **4.12** (Scheme 4.5a). In 2006 Trost and Zhang found that molybdenum and **4.13**[353,354] in comparison to palladium[355] provided superior enantioselectivities in the allylation of oxindoles (Scheme 4.5b).



Scheme 4.5 Representative protocols for catalytic C(3) functionalization of oxindoles.

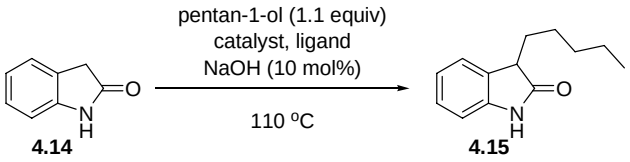
In contrast to these efficient catalytic procedures, the C(3) position is usually alkylated using stoichiometric amounts of base and alkyl halides. These processes are often hampered by poor regioselectivity and bisalkylation. Realizing this impediment we envisioned that the hydrogen autotransfer methodology would provide an efficient means to alkylate the C(3) position of oxindole in a catalytic and environmentally friendly manner. As detailed above oxindoles, specifically those containing C(3) functionalization represent an important motif in numerous natural products and pharmaceutical agents. Moreover, to the best of the author's knowledge this would constitute the first catalytic procedure for alkylating oxindoles.[a]

[a] Simultaneously with the publication of our work, Grigg and co-workers disclosed an iridium catalyzed C(3) alkylation of oxindole with alcohols. (Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron*, **2009**, *63*, 4375-4383).

4.2.2 Catalyst Optimization

Optimal reaction conditions were identified through a systematic study of various reaction parameters such as solvent, transition metal and ligand. The initial experiments focused on developing an efficient protocol for the direct alkylation of oxindole (**4.14**) with pentan-1-ol (Table 4.1). This system would provide a simple testing ground for a range of different catalysts.

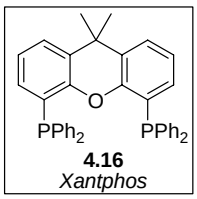
Table 4.1 Screening of alkylation catalysts.



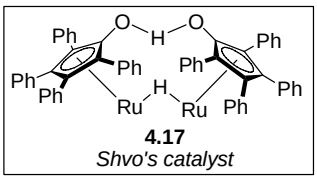
4.14 **4.15**

entry	catalyst	catalyst loading [mol%]	ligand	**4.15** (%)[b]
1	$[Cp^*IrCl_2]_2$	1.0	-	>95
2	$[IrCl(cod)]_2$	1.0	PPh_3	32[c]
3	$[RuCl_3 \cdot xH_2O]$	2.0	PPh_3	>95[c]
4	$[RuCl_3 \cdot xH_2O]$	2.0	-	0
5	$[RuCl_2(PPh_3)_3]$	2.0	-	>95
6	$[Ru(p\text{-cymene})Cl_2]_2$	1.0	-	47
7	$[Ru(p\text{-cymene})Cl_2]_2$	1.0	**4.16**	>95[d]
8	$[Ru(PPh_3)_3(CO)H_2]$	2.0	-	53
9	$[Ru(PPh_3)_3(CO)H_2]$	2.0	**4.16**	81[d]
10	**4.17**	1.0	-	>95
11	$[Ru(acac)_3]$	1.0	-	0

[a] Oxindole (2.0 mmol) was reacted with pentan-1-ol (2.2 mmol) under the influence of catalyst (1.0-2.0 mol%) and NaOH (10 mol%) at 110 °C for 20 h. [b] Conversion was estimated by ^1H NMR spectroscopy based oxindole. [c] PPh_3 (4.0 mol%). [d] Xantphos (2.0 mol%).



4.16
Xantphos



4.17
Shvo's catalyst

The characteristic C(3) protons of oxindole and the alkylated product offered a convenient method to monitor the reaction by ^1H NMR. Since the commercially available chloro-bridged iridium complex $[Cp^*IrCl_2]_2$ has recently found widespread use in hydrogen transfer processes we decided to employ it for this test reaction. The synthesis and catalytic activity of $[Cp^*IrCl_2]_2$ were originally disclosed by Maitlis and co-workers.[356-358] Fujita and co-workers have successfully deployed $[Cp^*IrCl_2]_2$ for the direct alkylation of secondary alcohols with primary alcohols,[359] whereas Grigg

and co-workers have selectively monoalkylated arylacetonitriles,[310] *tert*-butyl cyanoacetate,[311] and barbiturates[308] implementing $[Cp^*IrCl_2]_2$.

Initial experiments surveying a range of different bases, reaction temperatures, and solvents established that performing the reaction under neat conditions at 110 °C, in the presence of 1.0 mol% $[Cp^*IrCl_2]_2$ and 10 mol% NaOH in a sealed heavy-walled vial cleanly provided the 3-alkylation product **4.15** in almost quantitative yield (entry 1). Somewhat surprisingly, when $[IrCl(cod)]_2$ was deployed in combination with PPh_3 the desired product was only observed in 32% yield (entry 2). Ishii and co-workers[305] have previously utilized $[IrCl(cod)]_2$ and PPh_3 in combination with KOH or NaOH for the direct α-alkylation of ketones. Although $[Cp^*IrCl_2]_2$ presented itself as an effective catalyst for the selective C(3) alkylation of oxindole we decided to pursue a cheaper ruthenium based catalyst system.[a] When pentane-1-ol and oxindole **4.14** were heated in the presence of $[RuCl_3 \cdot xH_2O]$ and PPh_3 the desired product **4.15** was obtained cleanly within 20 h of stirring (entry 3).[b] The preformed complex $[RuCl_2(PPh_3)_3]$ performed equally well, whereas omitting PPh_3 led to complete recovery of the starting material (entries 4 and 5). The test reaction was subjected to a selection of other ruthenium based catalysts, which revealed that [Ru(*p*-cymene)$Cl_2]_2$ and $[Ru(PPh_3)_3(CO)H_2]$ in combination with xantphos (**4.16**) [312] as well as Shvo's catalyst[333] **4.17** furnished the desired product in high yield (entries 7, 9, and 10). Deploying $[Ru(acac)_3]$, $[Ru(PPh_3)_3(CO)H_2]$, and [Ru(*p*-cymene)$Cl_2]_2$ with no additional phosphine ligand afforded either relatively low conversion into the desired product or no reaction. Interestingly, competing *N*- or *O*-alkylation was not observed for any of the investigated catalyst systems. While several ruthenium based catalysts proved very effective in facilitating the desired alkylation of oxindole, we decided to settle for a mixture of $[RuCl_3 \cdot xH_2O]$ and PPh_3, which offered the simplest and cheapest alternative.[c]

With this catalyst system at hand we decided to conduct a number of experiments designed to investigate the influence of base and solvent in the alkylation reaction (Table 4.2). Sodium

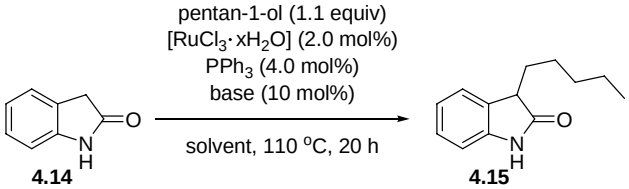
[a] For comparison: The price for $[RuCl_3 \cdot xH_2O]$ is 5.79 $/mmol while the price for $[IrCl_3 \cdot xH_2O]$ is 29.6 $/mmol (both based on anhydrous M_w). These prices were adopted from Aldrich on the 19th of June 2009.

[b] Monitoring the reaction by use of ^1H NMR revealed almost complete conversion within 12 h. Isolation of the alkylated product after 12 h and 20 h afforded **4.15** in 87% and 89%, respectively *i.e.* the product appeared to be stable under the reaction conditions.

[c] Changing the ratio between $[RuCl_3 \cdot xH_2O]$ and PPh_3 to 1:1 furnished a decrease in reaction rate, whereas a change to 1:3 had no significant influence on the rate.

hydroxide and potassium hydroxide seemed to perform equally well in the alkylation reaction (entries 1 and 2). Substituting NaOH with carbonates revealed a significant influence of the counterion. Both sodium and potassium carbonate failed to afford full conversion into **4.15**, whereas cesium carbonate cleanly furnished **4.15** (entries 3-5). Employing triethylamine also led to diminished yields of the desired product due to slow conversion of the starting material. In the absence of base the starting material was isolated in quantitatively, which is not surprising since the putative Knoevenagel-type condensation between the *in situ* generated aldehyde and oxindole is facilitated by base. Moreover, Bäckvall and Chowdhury[360] reported on the effect of base on the $[RuCl_2(PPh_3)_3]$-catalyzed transfer hydrogenation. It was observed that the addition of a catalytic amount of base afforded a rate enhancement of about 10^3-10^4 times.

Table 4.2 Screening of solvent and base.



entry	base	solvent	**4.15** (%)[b]
1	NaOH	-	>95
2	KOH	-	>95
3	Na_2CO_3	-	58
4	K_2CO_3	-	80
5	Cs_2CO_3	-	>95
6	Et_3N	-	39
7	-	-	0
8	NaOH	toluene	>95[c]
9	NaOH	*p*-dioxane	92[c]
10	NaOH	water	58[c]

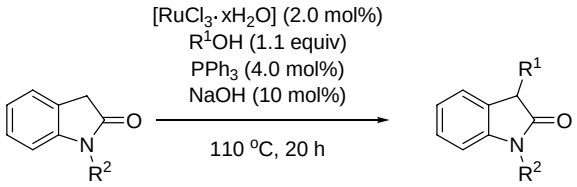
[a] Oxindole (2.0 mmol) was reacted with pentan-1-ol (2.2 mmol) under the influence of $RuCl_3$ xH_2O (2.0 mol%), PPh_3 (4.0 mol%), and base (10 mol%) at 110 °C for 20 h. [b] Conversion was estimated by ^1H NMR spectroscopy based oxindole. [c] Solvent (1.0 mL) added.

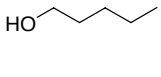
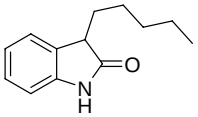
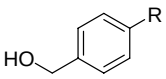
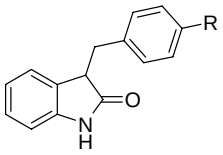
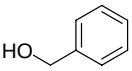
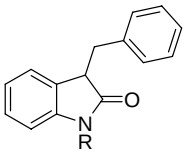
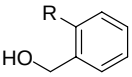
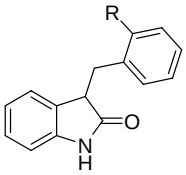
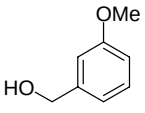
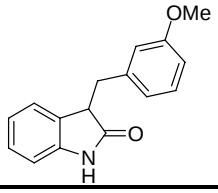
With a fully developed system in hand, our focused shifted toward developing a practical isolation procedure. We found that simple dilution of the crude reaction mixture utilizing CH_2Cl_2 followed by treatment with silica-gel and removal of residual solvent under high vacuum furnished a powder that was easily purified over silica gel providing the products in high yield.

4.2.3 Scope and Limitations

At this stage we commenced an exploration of the substrate scope of the reaction (Table 4.3 and 4.4). The C(3) alkylation of oxindole was general for a wide range of *o*-, *m*- and *p*-substituted benzyl alcohols. Most notable is the tolerance of one *o*-substituent, which would provide significant steric hindrance to the catalyst during the hydrogen transfer process. Alkyl substituted benzyl alcohols and benzyl alcohol were excellent coupling partners (entries 2, 6 and 13). Also the pharmaceutically relevant fluorine substituents were tolerated (entries 3, 4, and 11).

Table 4.3 C(3) alkylation of oxindoles.



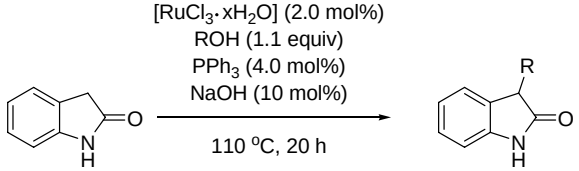
entry	alcohol	product		yield[b]
1				89
2			R = H	89
3			F	83
4			CF_3	86
5			Cl	89
6			Me	92
7			OMe	83
8			NHPiv	74[c]
9			Bn	91
10			PMB	92
11			F	81
12			Cl	88
13			Me	90
14			OMe	85
15				84

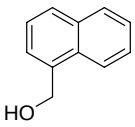
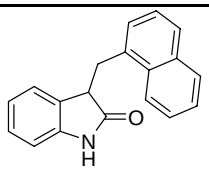
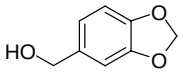
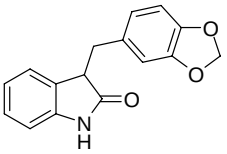
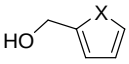
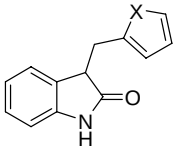
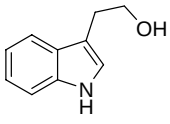
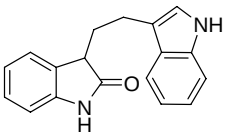
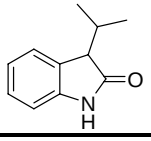
[a] The oxindole (2.0 mmol) was reacted with the alcohol (2.2 mmol) under the influence of $RuCl_3xH_2O$ (2.0 mol%), PPh_3 (4.0 mol%), and base (10 mol%) at 110 °C for 20 h. [b] Isolated yield. [c] Toluene (1.0 mL) used as cosolvent.

Importantly, aryl chlorides were compatible with the alkylation protocol providing a useful chemical handle for further manipulations. Biologically important methoxy substituents *o*, *m* or *p* were also well tolerated. Moreover, a selection of protecting groups such as amide, benzyl and *p*-methoxybenzyl were compatible with the reaction conditions. It should be noted that Boc-protection of the oxindole nitrogen afforded low conversion due to competing decarboxylation.

A naphthalene alcohol also proved compatible with the alkylation protocol affording the desired product in excellent isolated yield (entry 1, Table 4.4). A variety of pharmacophoric functionalities including catechol, furan, thiophene, and unprotected indole allowed for efficient alkylation of oxindole (entries 2-5).

Table 4.4 C(3) alkylation of oxindoles employing heteroaromatic and secondary alcohols.



entry	alcohol	product		yield[b]
1				87
2				79
3			X = O	71[c]
4			S	81
5				72[c]
6				73[d]

[a] Oxindole (2.0 mmol) was reacted with the alcohol (2.2 mmol) under the influence of $RuCl_3xH_2O$ (2.0 mol%), PPh_3 (4.0 mol%), and base (10 mol%) at 110 °C for 20 h. [b] Isolated yield. [c] Toluene (1.0 mL) used as cosolvent. [d] Stirred for 48 h with 5 equiv (10 mmol) of the alcohol.

Interestingly, attempts to alkylate oxindole with 2-hydroxymethylfuran under the standard neat reaction conditions primarily afforded decomposition, whereas addition of toluene furnished smooth conversion into the desired product. Initial experiments employing propan-2-ol in the alkylation procedure were met with limited success affording mixtures of the desired product and the α,β-unsaturated condensation product as well as unreacted oxindole. However, stirring oxindole with an excess of propan-2-ol (5 equiv) at 110 ^{o}C for 48h afforded full conversion and the desired product was isolated in 73% yield (entry 6).

Several substrates either failed completely to provide the corresponding alkylated product or only led to trace amounts of the desired product (Figure 4.3). The highly congested 2,6-dimethoxybenzyl alcohol **4.18** and 2,4,6-trimethylbenzyl alcohol **4.19** afforded the desired product in less than 25% yield as judged by ^{1}H NMR even after prolonged heating at elevated temperatures *i.e.* 20 h stirring at 180 ^{o}C instead of 110 ^{o}C. Subjecting the pentafluorobenzyl alcohol **4.20** to the standard alkylation conditions gave the desired alkylation product in less than 5%. Using 4-bromobenzyl alcohol **4.21** as well as 4-(hydroxymethyl)benzonitrile **4.22** furnished complex reaction mixtures. This can most likely be ascribed to hydrodehalogenation and hydrolysis, respectively. In order to circumvent problems caused by *in situ* hydrolysis of the nitrile functionality it was attempted to employ Cs_2CO_3 for the alkylation, however, this did not resolve the problem.

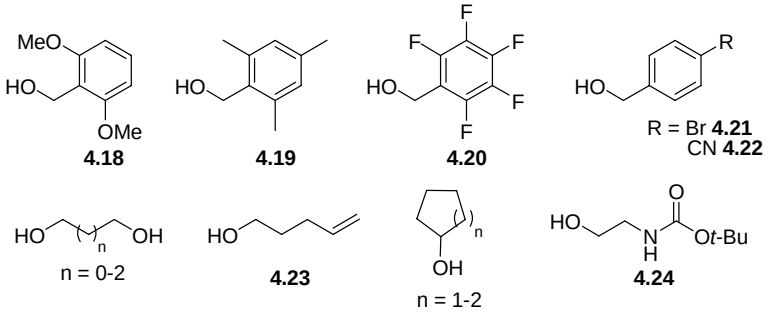
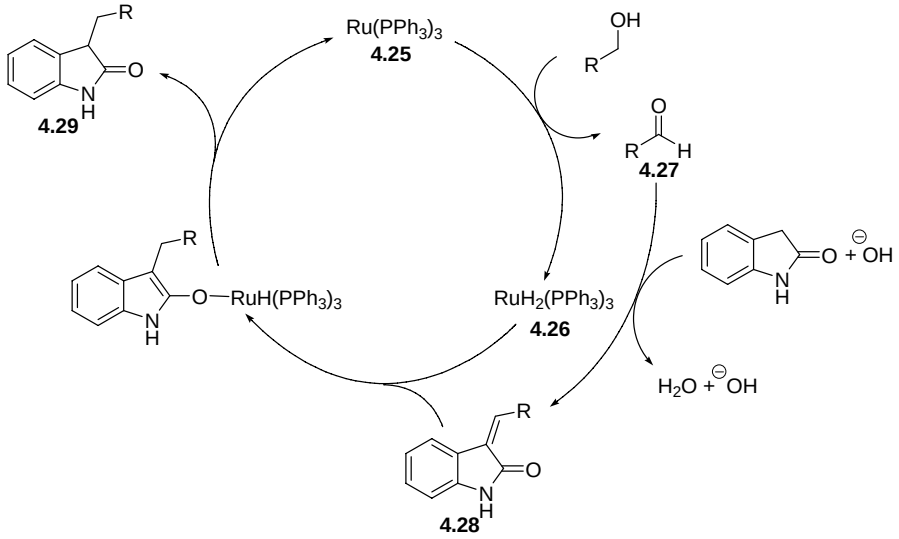


Figure 4.3 Substrates failing to furnish efficient C(3) alkylation of oxindole.

Furthermore a range of α,ω-diols were tested for the alkylation procedure, since these alcohols would afford a chemical handle for further manipulations. Unfortunately, α,ω-diols furnished only trace amount of the desired product and generally ^{1}H NMR as well as GC/MS of the crude reaction mixture were messy. When 4-penten-1-ol (**4.23**) was employed, a 2:1 mixture of **4.15** and the corresponding α,β-unsaturated oxindole was attained in a modest 27% yield. All attempts to deploy

cyclohexanol and cyclopentanol in the alkylation protocol gave inseparable mixtures of the α,β-unsaturated condensation product and the desired product. Thus for secondary alcohols the reduction of the putative intermediate α,β-unsaturated carbonyl species appears to be the rate-limiting step. Recognizing the biological importance of the 3,3'-pyrrolidinyl-spirooxindole motif we decided to explore the utility of carbamate **4.24** in the alkylation procedure. To our dismay all efforts to facilitate alkylation and subsequent cyclization deploying **4.24** were unfruitful furnishing less than 10% conversion of the starting material. This may most likely be ascribed to **4.24** chelating to ruthenium thus acting as a catalyst sink shutting down the catalytic cycle.

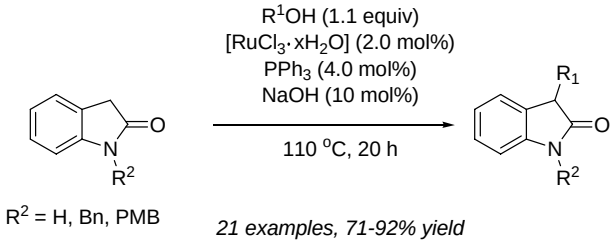
Bäckvall and co-workers[360] have previously shown that the active catalyst when utilizing $RuCl_2(PPh)_3$ for transferhydrogenation is most likely RuH_2PPh_3. Starting from $[RuCl_3 \cdot xH_2O]$ and PPh_3 it is reasonable to assume that this active catalyst is formed *in situ*.[360] Based on this assumption and the observations that base is a necessary additive, and the intermediate α,β-unsaturated carbonyl could be isolated in certain cases a mechanism is tentatively proposed (Scheme 4.6). A coordinatively unsaturated complex **4.25** is formed *in situ* and upon coordination of alcohol and β-hydride elimination a dihydride species **4.26** is formed along with the aldehyde **4.27**. This aldehyde possibly leaves the coordination sphere of ruthenium before undergoing a base mediated condensation with oxindole. Ultimately, the α,β-unsaturated oxindole **4.28** is reduced by the ruthenium dihydride complex **4.26** affording the saturated product **4.29** and regenerating the active catalyst **4.25**.



Scheme 4.6 Tentative mechanism for the ruthenium catalyzed alkylation.

4.3 Summary

We have developed an efficient protocol based on a hydrogen autotransfer process to directly alkylate the C(3) position of oxindole (Scheme 4.7). While several iridium and ruthenium catalyst proved to efficiently mediate this transformation we settled for the very cheap ruthenium source [$RuCl_3 \cdot xH_2O$] in combination with PPh_3 and sodium hydroxide. The reaction required in general 2.0 mol% of [$RuCl_3 \cdot xH_2O$], 4.0 mol% of PPh_3 and 10 mol% of sodium hydroxide to afford full conversion at 110 °C under neat reaction conditions. This procedure provides a relatively simple and highly atom-economical alternative to traditional alkylation procedures involving stoichiometric amount of base and alkyl halides.



Scheme 4.7 Ruthenium-catalyzed C(3) alkylation of oxindoles.

The reaction was highly selective for the formation of C(3) substituted oxindole. Moreover, this transformation was tolerant towards a relatively wide range of functional groups and could be applied to *o*-, *m*-, and *p*-substituted benzyl alcohols, several aromatic heterocycles, primary and secondary alcohols. This straightforward procedure allows for the synthesis of biologically important oxindoles starting from readily available oxindoles and alcohols.

4.4 Experimental Procedures

4.4.1 Materials and Methods

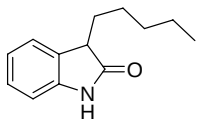
See chapter 2.7.1 for general experimental information.

4.4.2 Synthesis of 3-Alkylated Oxindoles

General Method for 3-Alkylation of Oxindole

[$RuCl_3 \cdot xH_2O$] (8.3 mg, 0.04 mmol), PPh_3 (21.0 mg, 0.08 mmol), NaOH (8.0 mg, 0.2 mmol), oxindole (266 mg, 2.0 mmol), and the alcohol (2.2 mmol) were placed in a 7-mL thick-walled screw-cap vial. The vial was purged with Ar and sealed with a screw-cap. The mixture was placed in an aluminum block preheated to 110 °C and stirred for 20 h or until ^{1}H NMR of the crude reaction mixture showed complete consumption of the oxindole. The reaction mixture was allowed to cool to room temperature followed by dilution with CH_2Cl_2 (10 mL). SiO_2 was added and the suspension was concentrated under reduced pressure to afford a powder that was purified by use of silica-gel chromatography (3 x 15cm SiO_2, 9:1→4:1→3:7 *n*-Hexane:EtOAc).

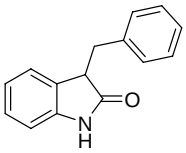
3-Pentyl-1,3-dihydro-indol-2-one (4.15) [Table 4.3, Entry 1]



Isolated yield: 89%

Colorless oil; R_f = 0.18 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (br s, 1H), 7.26-7.17 (m, 2H), 7.08-6.98 (m, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.48 (t, *J* = 5.9 Hz, 1H), 2.28-1.86 (m, 2H), 1.55-1.16 (m, 6H), 0.88 (t, *J* = 6.94 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.8, 141.6, 129.9, 127.7, 124.1, 122.2, 109.7, 46.1, 31.8, 30.5, 25.4, 22.4, 14.0; IR (Neat) 3211, 3094, 3060, 3031, 2955, 2928, 2858, 1701, 1620, 1470, 1338, 1219, 1100, 749 cm^{-1}; HRMS (ESI+) calc'd for $C_{15}H_{21}N_2O$ ($[M+H+MeCN]^+$) 245.1654, found 245.1649.

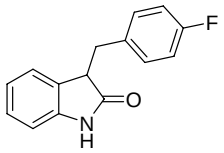
3-Benzyl-1,3-dihydro-indol-2-one [Table 4.3, Entry 2]



Isolated yield: 89%

Pale yellow needles; mp. 129-130 °C (heptane:EtOAc), Lit.[361] 129-131 °C; R_f = 0.12 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.30-7.11 (m, 6H), 6.90 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 3.76 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.50 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.95 (dd, *J* = 13.7, 9.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.9, 141.4, 137.8, 129.4, 128.9, 128.3, 127.9, 126.6, 124.8, 122.0, 109.7, 47.5, 36.6; IR (Neat) 3207, 3086, 3028, 2921, 2893, 1701, 1619, 1469, 1402, 1304, 1228, 1154, 749, 697 cm^{-1}, MS: *m/z* 223 [M]. Spectral data in accordance with literature values.[362]

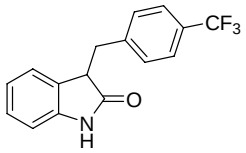
3-(4-Fluoro-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 3]



Isolated yield: 83%

Colorless needles; mp. 151-152 °C (heptane:EtOAc); R_f = 0.11 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.17 (ddt, *J* = 7.6, 1.4, 0.8 Hz, 1H), 7.14-7.05 (m, 2H), 6.97-6.86 (m, 3H), 6.86-6.78 (m, 2H), 3.72 (dd, *J* = 8.5, 4.6 Hz, 1H), 3.41 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.01 (dd, *J* = 13.8, 8.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.6, 161.7 (d, *J* = 245 Hz), 141.8, 133.2 (d, *J* = 3.2 Hz), 130.8 (d, *J* = 7.9 Hz), 128.6, 128.1, 124.6, 122.1, 115.1 (d, *J* = 21.2 Hz), 109.8, 47.6, 35.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.69 (dd, *J* = 9.0, 4.9 Hz, 1F); IR (Neat) 3210, 3092, 3071, 2927, 2892, 1707, 1620, 1601, 1509, 1471, 1300, 1224, 831, 751 cm^{-1}; HRMS (ESI+) calc'd for $C_{15}H_{13}FNO$ ($[M+H]^+$) 242.0981, found 242.0987.

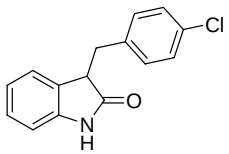
3-(4-Trifluoromethyl-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 4]



Isolated yield: 86%

Colorless needles; mp. 112-113 °C (heptane:EtOAc); R_f = 0.092 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.24-7.14 (m, 1H), 6.95 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.88-6.81 (m, 2H), 3.78 (dd, *J* = 8.5, 4.7 Hz, 1H), 3.49 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.09 (dd, *J* = 13.8, 8.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.2, 141.7, 141.4, 129.7, 129.0 (q, *J* = 32.4 Hz), 128.3, 128.3, 125.2 (q, *J* = 3.8 Hz), 124.6, 124.1 (q, *J* = 271.9 Hz), 122.2, 109.9, 47.1, 36.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.82 (s, 3F); IR (Neat) 3207, 3093, 3062, 3031, 2929, 2894, 2839, 1706, 1620, 1471, 1418, 1323, 1230, 1164, 1120, 1109, 1067, 1019, 836, 751 cm^{-1}; HRMS (ESI+) calc'd for $C_{18}H_{16}F_3N_2O$ ($[M+H+MeCN]^+$) 333.1215, found 333.1207.

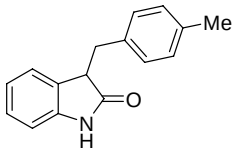
3-(4-Chloro-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 5]



Isolated yield: 89%

Pale yellow crystals; mp. 138-140 °C (heptane:EtOAc); R_f = 0.11 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.20-7.15 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 3.73 (dd, *J* = 8.5, 4.6 Hz, 1H), 3.41 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.99 (dd, *J* = 13.8, 8.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.4, 141.4, 136.0, 132.5, 130.7, 128.5, 128.4, 128.1, 124.6, 122.1, 109.8, 47.3, 35.8; IR (Neat) 3211, 3090, 3062, 3030, 2924, 2859, 1704, 1620, 1491, 1470, 1408, 1337, 1302, 1228, 1196, 1155, 1093, 1016, 825 cm^{-1}; HRMS (ESI+) calc'd for $C_{15}H_{13}ClNO$ ($[M+H]^+$) 258.0686, found 258.0681.

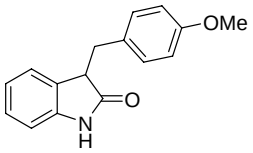
3-(4-Methyl-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 6]



Isolated yield: 92%

White powder; mp. 149-150 °C (heptane:EtOAc); R_f = 0.11 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.16 (ddt, *J* = 7.7, 1.2, 0.8 Hz, 1H), 7.06 (br s, 4H), 6.90 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.84-6.76 (m, 2H), 3.73 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.45 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.91 (dd, *J* = 13.7, 9.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.0, 141.5, 136.1, 134.6, 129.2, 129.1, 129.0, 127.8, 124.8, 121.9, 109.8, 47.6, 36.2, 21.0; IR (Neat) 3204, 3091, 3056, 3024, 2921, 2858, 1702, 1619, 1515, 1485, 1470, 1408, 1228, 1101, 814, 749 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{16}NO$ ($[M+H]^+$) 238.1231, found 238.1232.

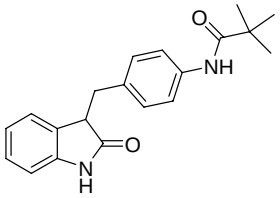
3-(4-Methoxy-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 7]



Isolated yield: 83%

Colorless needles; mp. 110-111 °C, Lit.[363] 114 °C; R_f = 0.07 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 7.21-7.13 (m, 1H), 7.13-7.02 (m, 2H), 6.91 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 2H), 6.80-6.72 (m, 2H), 3.77 (s, 3H), 3.71 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.42 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.92 (dd, *J* = 13.8, 8.9 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.3, 158.5, 141.8, 130.6, 129.9, 129.3, 128.2, 125.0, 122.2, 113.9, 110.1, 55.4, 48.1, 36.0; IR (Neat) 3194, 3091, 3059, 3032, 3011, 2953, 2932, 2915, 2835, 1703, 1615, 1511, 1470, 1441, 1337, 1301, 1246, 1101, 1034, 828, 750 cm^{-1}, MS: *m/z* 253 [M].

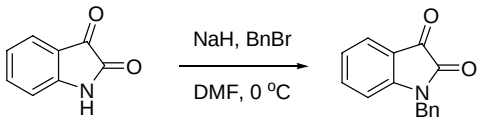
2,2-Dimethyl-*N*-[4-(2-oxo-2,3-dihydro-1*H*-indol-3-ylmethyl)-phenyl]-propionamide [Table 4.3, Entry 8]



Isolated yield: 74%

White powder; mp. 212-214 °C (CH_3CN); R_f = 0.48 (CH_2Cl_2:CH_3OH = 9:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (br s, 1H), 9.08 (br s, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 7.2 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 3.75 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.25 (dd, *J* = 13.7, 5.0 Hz, 1H), 2.91 (dd, *J* = 13.7, 7.5 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 178.1, 176.2, 142.6, 137.5, 132.6, 129.2, 128.9, 127.5, 124.3, 120.9, 119.9, 109.1, 46.5, 34.6, 27.2; IR (Neat) 3321, 3201, 3108, 3029, 2962, 2923, 2874, 2816, 1698, 1659, 1601, 1514, 1470, 1411, 1322, 1241, 925, 828, 749; HRMS (ESI+) calc'd for $C_{20}H_{23}N_2O_2$ ($[M+H]^+$) 323.1752, found 323.1756.

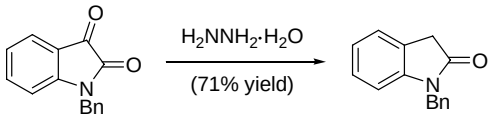
1-Benzyl isatin[364]



Isatin (2.94 g, 20 mmol) was placed in a 250 mL round bottom flask and dissolved in DMF (37 mL). The resulting bright orange solution was cooled to 0 °C by the use an ice/water bath. NaH (55% dispersion in mineral oil, 916 mg, 21 mmol) was added portionwise resulting in a deep purple solution. The solution was stirred until any effervescence had ceased (~15 min). Benzyl bromide (4.10 g, 2.85 mL, 24 mmol) was added in a dropwise manner and the resulting red-brown mixture was stirred for an additional 30 min at 0 °C. H_2O (176 mL) was added to precipitate the product. The product was filtered and recrystallized from EtOH. Yield 3.52 g (74%) of the title product as orange needles: mp. 129-130 °C (EtOH), Lit.[365] 133-135 °C (EtOH:H_2O); R_f = 0.66 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 7.62 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.48 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.41-7.27 (m, 5H), 7.09 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.79-6.75 (m, 1H), 4.94 (s, 2H); ^{13}C NMR (75.4 MHz), $CDCl_3$ δ 183.2, 158.2, 150.6, 138.3, 134.4, 129.0, 128.1, 127.4, 125.3, 123.8, 117.6, 111.0, 44.0; IR

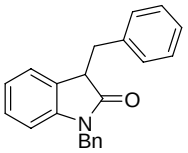
(Neat) 3062, 3031, 2954, 2929, 1736, 1612, 1496, 1470, 1437, 1350, 1177, 1096 cm^{-1}, MS: *m/z* 237 [M]. Spectral data in accordance with literature values.[364]

1-Benzyl-1,2-dihydro-indol-2-one[364]



1-Benzyl isatin (2.37 g, 10 mmol) was suspended in hydrazine hydrate (11 mL) and the mixture was heated to reflux until the gas evolution had stopped (4 h). The reaction mixture went from orange via green to yellow within this time. The reaction mixture was allowed to cool to ambient temperature and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude yellow product was recrystallized from Et_2O. Yield 1.59 g (71%) of the title compound as off-white needles: mp. 67-68 °C (Et_2O), Lit.[366] 68 °C (Et_2O); R_f = 0.29 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.24 (m, 6H), 7.22-7.11 (m, 1H), 7.01 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 4.92 (s, 2H), 3.63 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.1, 144.2, 135.8, 128.7, 127.7, 127.5, 127.3, 124.4, 124.3, 122.3, 109.0, 43.7, 35.7; IR (Neat) 3087, 3057, 3032, 2945, 2918, 1700, 1613, 1487, 1466, 1378, 1225, 1196, 1165, 748, 725 cm^{-1}, MS: *m/z* 223 [M]. Spectral data in accordance with literature values.[364]

1,3-Dibenzyl-1,3-dihydro-indol-2-one [Table 4.3, Entry 9]

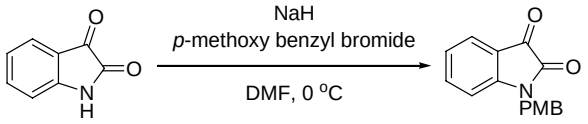


Isolated yield: 91%

White powder; mp. 97-98 °C (*n*-hexane:EtOAc); R_f = 0.36 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.07 (m, 9H), 7.01-6.88 (m, 4H), 6.55 (d, *J* = 7.7 Hz, 1H), 5.04 (d, *J* = 15.8 Hz, 1H), 4.64 (d, *J* = 15.8 Hz, 1H), 3.86 (dd, *J* = 8.1, 4.3 Hz, 1H), 3.51 (dd, *J* = 13.5, 4.3 Hz, 1H), 3.14 (dd, *J* = 13.5, 8.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.8, 143.3, 137.3, 135.5, 129.6, 128.6, 128.2, 128.1, 127.9, 127.3, 126.8, 126.6, 124.4, 122.1, 109.0, 47.0, 43.5, 36.4; IR (Neat)

3106, 3086, 3060, 3029, 2919, 1711, 1613, 1489, 1466, 1361, 1187, 751, 698 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{20}NO$ ($[M+H]^+$) 314.1545, found 314.1541.

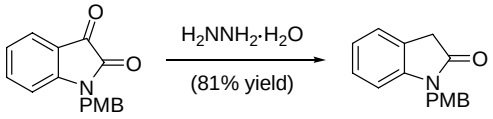
1-(4-Methoxy-benzyl)-1*H*-indole-2,3-dione



(85% yield)

Isatin (2.94 g, 20 mmol) was placed in a 250 mL round bottom flask and dissolved in DMF (37 mL). The resulting bright orange solution was cooled to 0 °C by the use an ice/water bath. NaH (55% dispersion in mineral oil, 916 mg, 21 mmol) was added portionwise resulting in a deep purple solution. The solution was stirred until any effervescence had ceased (~15 min). *para*-Methoxy benzyl bromide (4.83 g, 3.46 mL, 24 mmol) was added in a dropwise manner and the resulting red-brown mixture was stirred for an additional 30 min at 0 °C. H_2O (176 mL) was added to precipitate the product. The product was filtered and recrystallized from EtOH. Yield 4.55 g (85%) of the title compound as orange needles: mp. 161-162 °C (EtOH), Lit.[367] 171-172 °C; R_f = 0.65 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 7.5, 1.3, 0.6 Hz, 1H), 7.48 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.29-7.26 (m, 2H), 7.08 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.90-6.84 (m, 2H), 6.80 (br d, *J* = 8.0 Hz, 1H), 4.87 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 183.3, 159.3, 158.1, 150.7, 138.2, 128.8, 126.4, 125.3, 123.7, 117.6, 114.3, 111.0, 55.2, 43.4; IR (Neat) 3087, 3057, 3032, 2945, 2918, 1700, 1613, 1487, 1466, 1344, 1225, 1196, 1165, 748, 725, 697 cm^{-1}, MS: *m/z* 267 [M]. Spectral data in accordance with literature values.[368]

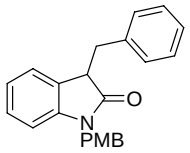
1-(4-Methoxy-benzyl)-1,3-dihydro-indol-2-one



1-(4-Methoxy-benzyl)-1*H*-indole-2,3-dione (2.67 g, 10 mmol) was suspended in hydrazine hydrate (11 mL) and the mixture was heated to reflux until the gas evolution had stopped (4 h). The reaction mixture went from orange via green to yellow within this time. The reaction mixture was allowed to cool to ambient temperature and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude yellow

product was recrystallized from EtOH. Yield 2.07 g (81%) of the title compound as pale yellow needles: mp. 105-106 °C (EtOH), Lit.[367] 103-104 °C; R_f = 0.21 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.22 (m, 4H), 7.21-7.13 (m, 1H), 7.00 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.87-6.80 (m, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 4.85 (s, 2H), 3.77 (s, 3H), 3.60 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0, 159.0, 144.3, 128.7, 127.9, 127.7, 124.4, 124.3, 122.2, 114.0, 109.0, 55.2, 43.1, 35.7; IR (Neat) 3055, 3036, 2999, 2954, 2932, 2915, 2836, 1698, 1612, 1511, 1487, 1438, 1378, 1276, 1175, 1165, 1031, 748 cm^{-1}, MS: *m/z* 253 [M]. Spectral data in accordance with literature values.[369]

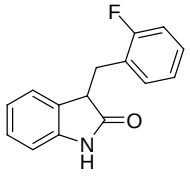
3-Benzyl-1-(4-methoxy-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 10]



Isolated yield: 92%

Pale yellow oil; R_f = 0.18 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.19 (m, 3H), 7.17-7.04 (m, 3H), 6.98-6.85 (m, 4H), 6.79-6.69 (m, 2H), 6.58 (d, *J* = 7.8 Hz, 1H), 4.97 (d, *J* = 15.5 Hz, 1H), 4.59 (d, *J* = 15.5 Hz, 1H), 3.83 (dd, *J* = 8.2, 4.3 Hz, 1H), 3.76 (s, 3H), 3.50 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.11 (dd, *J* = 13.6, 8.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.8, 158.8, 143.4, 137.4, 129.6, 128.3, 128.2, 128.2, 127.8, 127.6, 126.5, 124.4, 122.0, 114.0, 109.0, 55.2, 47.0, 42.9, 36.4; IR (Neat) 3058, 3030, 3001, 2929, 2835, 1708, 1612, 1512, 1488, 1466, 1359, 1247, 1177, 1033, 750, 700 cm^{-1}; HRMS (ESI+) calc'd for $C_{23}H_{22}NO_2$ ($[M+H]^+$) 344.1651, found 344.1647.

3-(2-Fluoro-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 11]

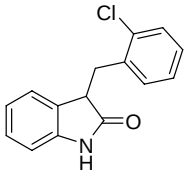


Isolated yield: 81%

Off-white needles; mp. 123-124 °C (heptane:EtOAc); R_f = 0.17 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 7.36-7.10 (m, 3H), 7.10-7.02 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.89 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.3 Hz, 1H), 3.80 (dd, *J* =

9.1, 5.2 Hz, 1H), 3.55 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.96 (dd, *J* = 13.9, 9.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.0, 161.2 (d, *J* = 245.9 Hz), 141.5, 131.5 (d, *J* = 4.5 Hz), 128.7, 128.5 (d, *J* = 8.1 Hz), 128.0, 125.1 (d, *J* = 15.3 Hz), 124.7, 123.9 (d, *J* = 3.6 Hz), 122.0, 115.3 (d, *J* = 22.1 Hz), 109.8, 46.1 (d, *J* = 1.4 Hz), 30.0 (d, *J* = 1.8 Hz); IR (Neat) 3208, 3087, 3061, 3032, 1700, 1619, 1599, 1490, 1469, 1456, 1337, 1304, 1229, 1185, 1100, 746 cm^{-1}; HRMS (ESI+) calc'd for $C_{15}H_{13}FNO$ ($[M+H]^+$) 242.0981, found 242.0987.

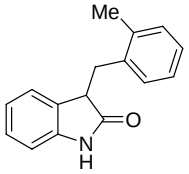
3-(2-Chloro-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 12]



Isolated yield: 88%

Pale yellow powder; mp. 89-91 °C (*n*-hexane:EtOAc); R_f = 0.17 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (br s, 1H), 7.33-7.17 (m, 1H), 7.15-6.94 (m, 4H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.70 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.44 (d, *J* = 5.5 Hz, 1H), 3.75 (dd, *J* = 9.9, 5.5 Hz, 1H), 3.47 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.80 (dd, *J* = 13.8, 9.9 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.7, 141.4, 135.9, 134.4, 131.9, 129.7, 128.8, 128.3, 128.0, 126.6, 124.9, 122.0, 109.8, 45.2, 34.8; IR (Neat) 3209, 3060, 2928, 1701, 1619, 1470, 1337, 1229, 1053, 908, 748, 676 cm^{-1}; HRMS (ESI+) calc'd for $C_{15}H_{13}ClNO$ ($[M+H]^+$) 258.0686, found 258.0693.

3-(2-Methyl-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 13]

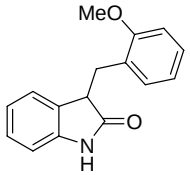


Isolated yield: 90%

Pale yellow needles; mp. 106-108 °C (heptane:EtOAc); R_f = 0.21 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.23-7.12 (m, 5H), 6.91-6.77 (m, 2H), 6.54 (d, *J* = 7.3 Hz, 1H), 3.71 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.52 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.82 (dd, *J* = 14.0, 10.9 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.2, 141.4, 136.7, 136.5, 130.5, 130.0, 129.1, 127.9, 126.8, 125.9, 125.0, 121.9, 109.8, 46.3, 34.3, 19.6; IR (Neat) 3192, 3077, 3061, 3021 2955,

2929, 1705, 1620, 1485, 1470, 1402, 1338, 1307, 1230, 749 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{16}NO$ ($[M+H]^+$) 238.1232, found 238.1227.

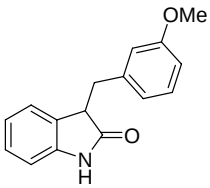
3-(2-Methoxy-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 14]



Isolated yield: 85%

Colorless needles; mp. 120-121 °C (heptane:EtOAc); R_f = 0.16 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.27 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.14 (tt, *J* = 7.7, 1.1 Hz, 1H), 7.11 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.92-6.80 (m, 4H), 6.54 (d, *J* = 7.4 Hz, 1H), 3.92 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.82 (s, 3H), 3.60 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.75 (dd, *J* = 13.4, 10.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.7, 157.7, 141.5, 131.4, 129.6, 128.1, 127.6, 126.5, 125.0, 121.6, 120.1, 110.2, 109.6, 55.1, 45.4, 32.2; IR (Neat) 3212, 3081, 3063, 3030, 2938, 2835, 1704, 1620, 1494, 1470, 1438, 1338, 1308, 1245, 1179, 1111, 1052, 1031 749 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{16}NO_2$ ($[M+H]^+$) 254.1181, found 254.1176.

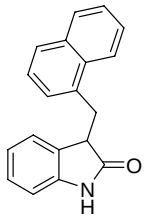
3-(3-Methoxy-benzyl)-1,3-dihydro-indol-2-one [Table 4.3, Entry 15]



Isolated yield: 84%

White powder; mp. 87-88 °C (hexane:EtOAc), Lit.[370] 87-88 °C (hexane:EtOAc); R_f = 0.19 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.17 (t, *J* = 7.9 Hz, 2H), 6.91 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.86-6.70 (m, 5H), 3.75 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.73 (s, 3H) 3.48 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.91 (dd, *J* = 13.7, 9.3 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.9, 159.4, 141.5, 139.3, 129.3, 128.9. 127.9, 124.8, 122.0, 121.7, 114.6, 112.3, 109.8. 55.1, 47.5, 36.6; IR (Neat) 3202, 3090, 3059, 3029, 2943, 2834, 1700, 1618, 1600, 1486, 1469, 1438, 1336, 1293, 1260, 1228, 1153, 751 cm^{-1}, MS: *m/z* 253 [M]. Spectral data in accordance with literature values.[370]

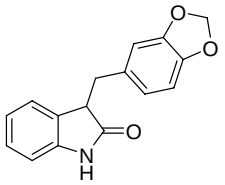
3-Naphthalen-1-ylmethyl-1,3-dihydro-indol-2-one [Table 4.4, Entry 1]



Isolated yield: 87%

Yellow needless; mp. 109-110 °C (hexane:EtOAc); R_f = 0.27 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 8.27 (d, *J* = 8.3 Hz, 1H), 7.98-7.91 (m, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.64-7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.32 (d, *J* = 6.9 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.81 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.42 (d, *J* = 7.5 Hz, 1H), 4.16 (dd, *J* = 13.9, 3.9 Hz, 1H), 3.92 (dd, *J* = 11.0, 3.9 Hz, 1H), 3.07 (dd, *J* = 13.9, 11.0 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.1, 141.4, 134.2, 134.0, 131.6, 129.4, 129.0, 127.9, 127.9, 127.8, 126.3, 125.8, 125.3, 125.1, 123.6, 121.9, 109.8, 46.3, 34.9; IR (Neat) 3204, 3060, 2945, 2892, 2836, 1700, 1620, 1598, 1469, 1306, 1018, 784, 751 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{16}NO$ ($[M+H]^+$) 274.1232, found 274.1232.

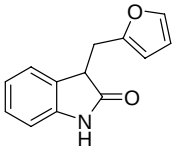
3-Benzo[1,3]dioxol-5-ylmethyl-1,3-dihydro-indol-2-one [Table 4.4, Entry 2]



Isolated yield: 79%

Pale yellow needles; mp. 135-136 °C (heptane:EtOAc); R_f = 0.10 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 7.18 (ddt, *J* = 7.7, 1.3, 0.8 Hz, 1H), 6.93 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 2.7 Hz, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 6.61 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.91 (s, 2H), 3.69 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.40 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.88 (dd, *J* = 13.8, 9.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.7, 147.5, 146.2, 141.4, 131.4, 128.8, 127.9, 124.7, 122.5, 122.0, 109.8, 109.6, 108.0, 100.8, 47.7, 36.4; IR (Neat) 3215, 3092, 3062, 3029, 2895, 1705, 1620, 1502, 1489, 1470, 1443, 1337, 1191, 1039, 933, 813, 751 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{14}NO_3$ ($[M+H]^+$) 268.0974, found 268.0967.

3-Furan-2-ylmethyl-1,3-dihydro-indol-2-one [Table 4.4, Entry 3]

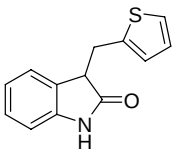


Isolated yield: 71%

Toluene (1.0 mL) was used as co-solvent.

White powder; mp. 146-147 °C (*n*-Hexane:EtOAc); R_f = 0.16 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.34 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.24-7.15 (m, 1H), 6.94 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.03 (dd, *J* = 3.2, 0.8 Hz, 1H), 3.81 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.48 (dd, *J* = 15.0, 4.6 Hz, 1H), 2.99 (dd, *J* = 15.0, 9.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.7, 151.9, 141.5, 141.4, 128.7, 128.0, 124.6, 122.2, 110.3, 109.8, 107.3, 45.2, 29.0; IR (Neat) 3182, 3150, 2964, 2902, 2839, 1699, 1619, 1470, 1341, 1263, 1230, 1008, 738 cm^{-1}; HRMS (ESI+) calc'd for $C_{13}H_{12}NO_2$ ($[M+H]^+$) 214.0868, found 214.0867.

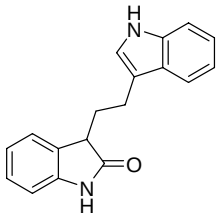
3-Thiophen-2-ylmethyl-1,3-dihydro-indol-2-one [Table 4.4, Entry 4]



Isolated yield: 81%

Yellow needles; mp. 154-155 °C (heptane:EtOAc); R_f = 0.22 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.23-7.18 (m, 1H), 7.10 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.04-6.93 (m, 2H), 6.89-6.74 (m, 3H), 3.76 (dd, *J* = 8.1, 4.4 Hz, 1H), 3.61 (ddd, *J* = 14.8, 4.4, 0.8 Hz, 1H), 3.34 (dd, *J* = 14.8, 8.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.8, 142.1, 140.0, 128.9, 128.6, 127.0, 126.8, 125.0, 124.7, 122.6, 110.3, 48.1, 31.0; IR (Neat) 3206, 3092, 3030, 2916, 2841, 1701, 1620, 1485, 1470, 1435, 1337, 1186, 750, 697 cm^{-1}; HRMS (ESI+) calc'd for $C_{13}H_{12}NOS$ ($[M+H]^+$) 230.0640, found 230.0638.

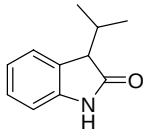
3-[2-(1*H*-Indol-3-yl)-ethyl]-1,3-dihydro-indol-2-one [Table 4.4, Entry 5]



Isolated yield: 72 %

Pale yellow oil; R_f = 0.47 (CH_2Cl_2:CH_3OH = 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.02 (br s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.35-7.32 (m, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.26-7.18 (m, 2H), 7.1 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dt, *J* = 7.6, 0.9 Hz, 1H), 6.98 (d, *J* = 2.3 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 3.59 (t, *J* = 6.0 Hz, 1H), 3.01-2.79 (m, 2H), 2.43-2.35 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.7, 141.6, 136.2, 129.7, 127.8, 127.3, 124.1, 122.3, 121.9, 121.5, 119.2, 118.8, 115.3, 111.0, 109.8, 45.6, 31.0, 21.4; IR (Neat) 3410, 3299, 3058, 2926, 2855, 1697, 1620, 1470, 1338, 1266, 1220, 1101, 909, 740 cm^{-1}; HRMS (ESI+) calc'd for $C_{18}H_{17}N_2O$ ($[M+H]^+$) 277.1341, found 277.1334.

3-Isopropyl-1,3-dihydro-indol-2-one [Table 4.4, Entry 6]



Isolated yield: 73%

10 mmol (5 equiv) isopropyl alcohol was used and the reaction was run for 48 h at 110 °C.

White powder; mp.108-109 °C (*n*-Hexane:EtOAc), Lit.[371] 105-106 °C; R_f = 0.23 (heptane:EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.29-7.17 (m, 2H), 7.01 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 3.40 (d, *J* = 3.5 Hz, 1H), 2.59-2.42 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 180.5, 142.1, 128.3, 127.7, 124.5, 122.0, 109.7, 52.2, 30.7, 19.9, 17.8; IR (Neat) 3172, 3139, 3063, 2959, 2872, 1692, 1616, 1470, 1414, 1344, 1297, 1220, 1182, 749 cm^{-1}; MS: *m/z* 175 [M]. Spectral data in accordance with literature values[347]

5 Studies Toward the Asymmetric Total Synthesis of Variecolin

5.1 Introduction

5.1.1 Isolation and Structural Determination

The sesterterpenoid variecolin (**5.1**) was first isolated in 1991 from the fermentation broth of *Aspergillus variecolor* at Merck Research Laboratories (Figure 5.1, **5.1** and **5.2**).[372] Based on 2D NMR spectroscopy variecolin (**5.1**) was shown to possess a novel [5-8-6-5]-tetracyclic skeleton with an AB *cis* ring fusion, BC and CD *trans* ring fusions, eight stereocenters (two of which are quaternary carbon centers contained in the C ring), and a central eight-membered B ring. From biosynthetic considerations Hensens and co-workers proposed the absolute configuration depicted in Figure 5.1.

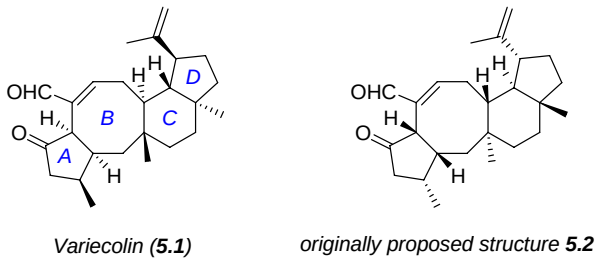
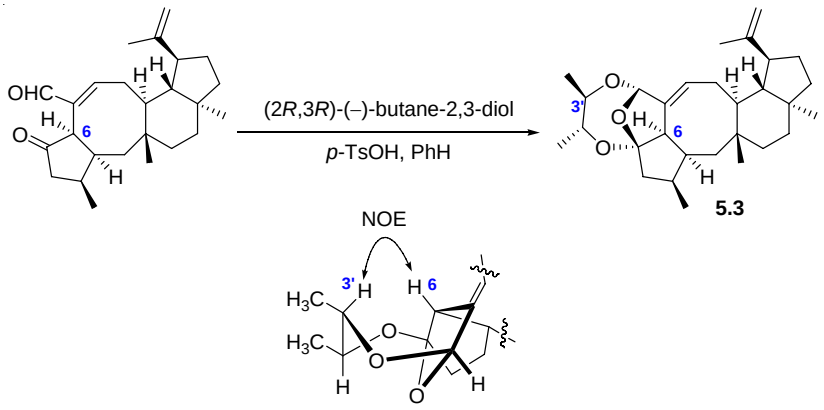


Figure 5.1 The tetracyclic sesterterpenoid variecolin (**5.1**).

The absolute configuration of variecolin (**5.1**), however, remained elusive until 2000, when Fujimoto and co-workers utilized HMBC NMR along with nuclear Overhauser effect (NOE) experiments to determine the absolute configuration of a (6*R*, 7*R*)-dimethyl-1,3,5-trioxacycloheptyl derivative of variecolin (**5.3**).[373] Variecolin (**5.1**) was treated with a chiral diol, (2*R*, 3*R*)-(–)-butane-2,3-diol under acidic conditions (Scheme 5.1). Analysis of the ensuing chiral bis-hemiketal **5.3** revealed a significant NOE between H(6) and H(3'), indicating that the absolute configuration at C(6) is *R*. Therefore the absolute configuration of variecolin is as depicted in structure **5.1**.



Scheme 5.1 Determination of the absolute configuration of variecolin (**5.1**).

Since the original discovery of variecolin (**5.1**) a family of congeners has also been identified (Figure 5.2).[373-375] In 1999 Kawai and co-workers[374] reported the isolation of variecolactone (**5.4**) and variecolol (**5.5**) from the mycelium of *Emericella purpurea*. Both variecolactone (**5.4**) and variecolol (**5.5**) contain the [5-8-6-5]-tetracyclic skeleton of variecolin (**5.1**). However, in the case of **5.4**, a 5-membered lactone is present while in the case of **5.5**, a 5-membered hemiketal ring exists. In addition, Kawai was able to obtain an X-ray crystal structure of variecolactone **5.4** confirming the relative structure.

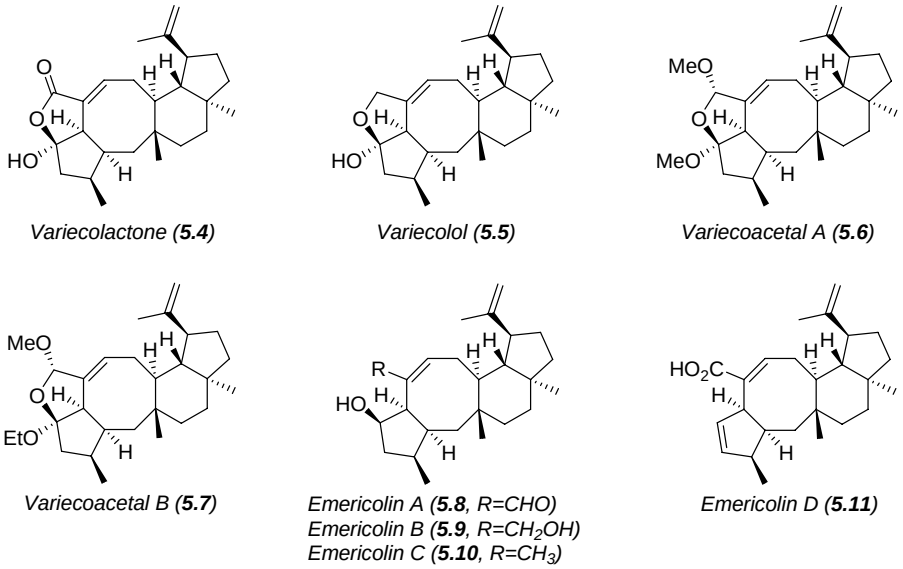


Figure 5.2 Members of the variecolin family of sesterterpenoids.

Later, Fujimoto and co-workers[373] disclosed two novel members of the variecolin family, variecoacetals A (**5.6**) and B (**5.7**). Both compounds were isolated from the fungus *Emericella*

aurantiobrunnea. Four additional members, emericolins A–D (**5.8**, **5.9**, **5.10**, and **5.11**, Figure 5.2) of the family were isolated from *Emericella aurantiobrunnea* in 2004 by Butler and co-workers.[375] Significantly, an X-ray crystal structure of variecolin (**5.1**) was attained for the first time, thus confirming the relative stereochemistry.

5.1.2 Biological Activity

The sesterterpenoid variecolin (**5.1**) has shown a broad range of biological activity since its isolation in 1991. In the original isolation paper Hensens and co-workers[372] showed that variecolin (**5.1**) is an angiotension II receptor antagonist, which is a crucial receptor target in the treatment of hypertension (high blood pressure). Later, the immunosuppressive activities (IC_{50} values) of variecolin (**5.1**) and several of its congeners against Con A (T-cells) and LPS (B-cells) induced proliferation of mouse splenic lymphocytes were studied by Fujimoto.[373,376]

Table 5.1 Immunosuppressive effects of variecolin (**5.1**) and congeners **5.4**, **5.5**, **5.6**, and **5.7** compared to azathioprine, cyclosporine A, and FK506 on the Con A-induced and LPS-induced proliferation of mouse splenic lymphocytes

	IC_{50} (μg/mL)	
Compound	Con A-induced	LPS-induced
Variecolin (**5.1**)	0.4	0.1
Variecolol (**5.5**)	1.7	0.6
Variecolactone (**5.4**)	8.0	2.5
Variecoacetal A (**5.6**)	4.5	1.5
Variecoacetal B (**5.7**)	6.5	2.2
Azathioprine	2.7	2.7
Cyclosporine A	0.04	0.07
FK506	1.5×10^{-5}	1.6×10^{-3}

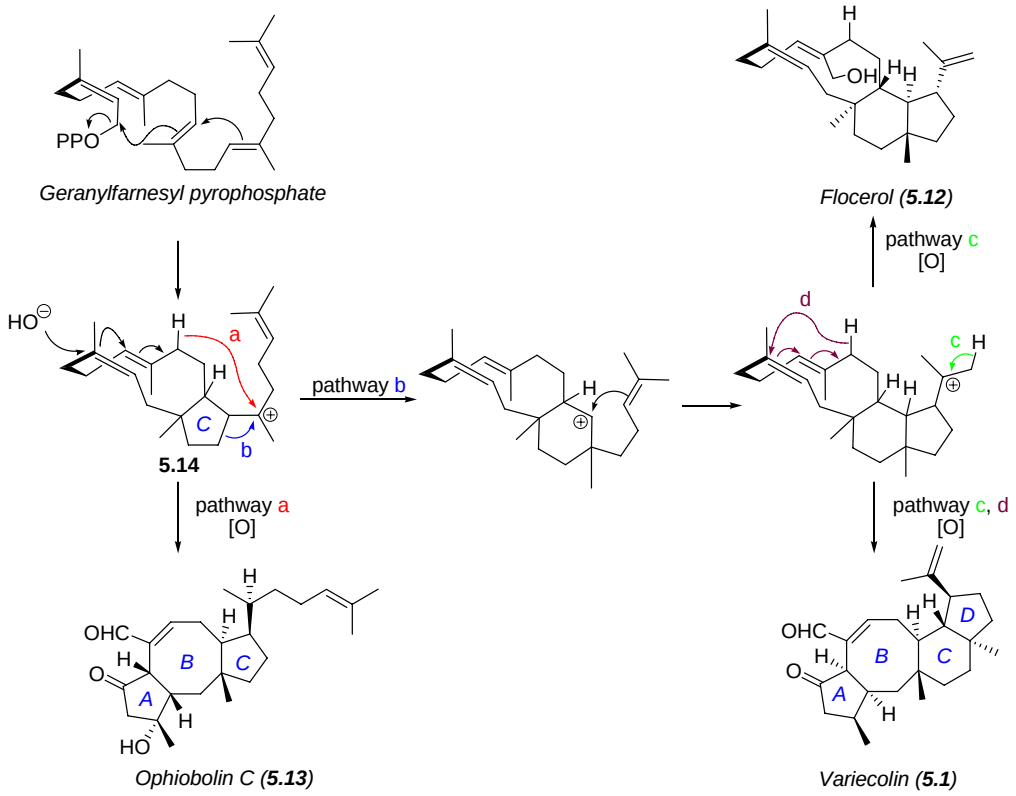
Variecolin (**5.1**) displayed the highest immunosuppressive activity rivaling those of commercial drugs azathioprine and cyclosporine A. **5.1** is an order of magnitude more active than its congeners (**5.4**-**5.7**) indicating the significance of the conjugated aldehyde at C(20) and the ketone at C(5) for the biological activity. Immunosuppressants are of crucial importance as a countermeasure to acute rejection of new organ(s) after transplantation and in the treatment of autoimmune diseases such as multiple sclerosis.

Most recently, Butler and co-workers[375] have reported that variecolin (**5.1**) and variecolactone (**5.4**) are antagonists for the CCR5 chemokine receptor (IC_{50} = 9 and 32 μM, respectively) while the emericolins A (**5.8**), B (**5.9**), C (**5.10**), and D (**5.11**) were inactive. Chemokines constitute a family

of intracellular messengers of importance for the development, homeostasis and immune response in the organism.[377] The chemokine receptors CCR5 and CXCR4 belong to the cellular G-protein-coupled system and mediate the physiological activities of the chemokines. Over the last decade, these receptors have presented themselves as novel targets for potential anti-HIV drugs.[378-382] The glycoprotein gp120 which is situated on the viral envelope of HIV-1 mediates attachment to the target cell (macrophages and T-cells) through the engagement of two cellular receptor molecules: the CD4 glycoprotein and a coreceptor, most often CCR5.[382] Since this coreceptor is a requisite for HIV-1 uptake, CCR5 presents itself as a prime target for new therapeutic agents. Perhaps more importantly genetic studies in EU subjects established that a 32 bp deletion within the coding region of the CCR5 gene (CCR5-Δ32) resulting in a non-functional receptor led to high resistance toward the R5-strain of HIV-1.[383,384] Strikingly, it was established that functional CCR5 receptors are not essential for immune competence which provide an important proof-of-principle of the potential safety of CCR5-targeted therapeutics.[385]

5.1.3 Proposed Biosynthesis

In the isolation paper Hensens and co-workers[372] proposed that the ABCD skeletal core of variecolin (**5.1**) can be traced back to the mevalonate biosynthetic pathway from geranylfarnesyl pyrophosphate (Scheme 5.2). Importantly, this proposal attempts to establish a biosynthetic linkage between variecolin (**5.1**) and prior knowledge about the structurally related classes of sesterterpenoids ceriferene (*e.g.* flocerol (**5.12**)) and ophiobolin (ophiobolin C (**5.13**)).[386-388] The proposed biosynthetic pathway commences with the loss of the labile diphosphate (-OPP) to form an allylic carbocation. This initiates a concerted cyclization reaction that generates the core C-ring fused to a macrocycle and a secondary carbocation **5.14**. Starting from this common intermediate two biosynthetic pathways diverge. The synthesis of the ophiobolins is triggered by a 1,5-hydride shift (pathway *a*) followed by oxidation to furnish ophiobolin C (**5.13**). The *trans*-fused CD-ring system of variecolin (**5.1**) and flocerol (**5.12**) is attained by a ring expansion via pathway *b* followed by a rapid cyclization. Subsequent *β*-hydride elimination installs the isopropenyl moiety of flocerol (**5.12**) and variecolin (**5.1**) (pathway *c*). Further oxidation provides flocerol as an [11-6-5] fused ring system. Alternatively, a concerted cyclization initiated by a 1,5-hydride shift generates the AB-ring-system of variecolin (**5.1**) (pathway *d*).



Scheme 5.2 Hensens proposal for the biosynthesis of variecolin (**5.1**).

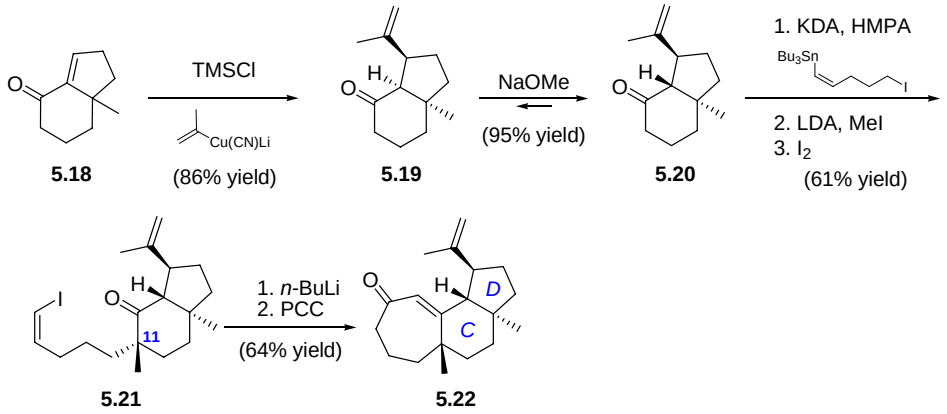
5.2 Previous Synthetic Efforts

Despite the interesting biological profile and complex unprecedented carbon skeleton variecolin (**5.1**) has only received scarce interest by the synthetic community. Hitherto no total synthesis has been reported and only two research groups have disclosed synthetic studies directed toward variecolin.

5.2.1 Piers' Sequential Annulation Approach

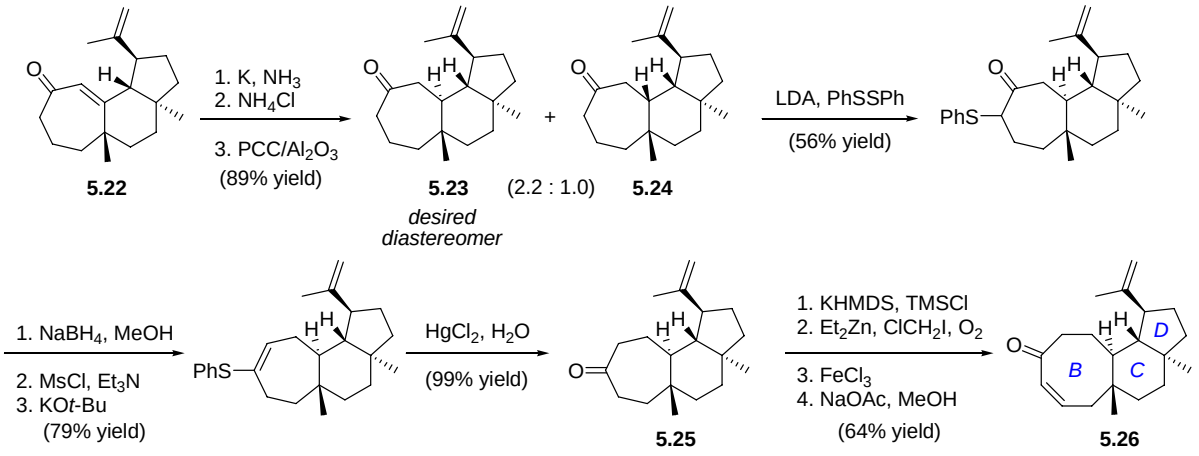
In 1997, six years after the first isolation of variecolin (**5.1**), Piers and Boulet revealed their interest in the variecolin family disclosing a route to the CD-ring system.[389] In his Ph.D. thesis from 2002,[390] Shawn Walker from the Piers research group reported the total synthesis of (±)-5-deoxyvariecolin (**5.15**), (±)-5-deoxyvariecolol (**5.16**), and (±)-5-deoxyvariecolactone (**5.17**) (cf. Scheme 5.5). The central design feature was to employ two sequential annulation protocols and a ring-expansion sequence to forge the carbon skeleton of variecolin (**5.1**). The synthesis commenced with the known ketone[391] **5.18** utilizing chemistry previously developed in the Piers laboratory (Scheme 5.3).[389]

TMSCl-accelerated conjugate addition of a higher order cuprate afforded the undesired *cis*-fused ketone **5.19** exclusively. This could, however, easily be rectified by treating *cis*-ketone **5.19** with NaOMe in MeOH providing a 14:1 ratio of the desired bicyclic *trans*-ketone **5.20** to *cis*-ketone **5.19** in excellent yield.[392,393]



Scheme 5.3 Preparation of the ring-expansion precursor.

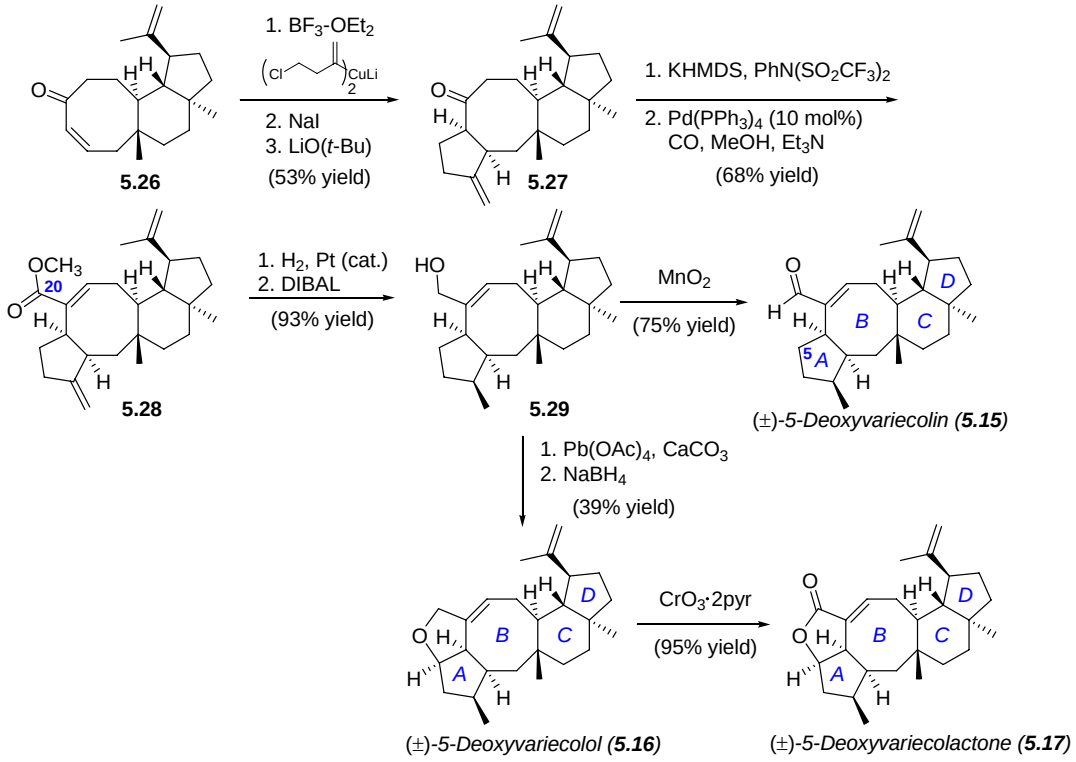
The quaternary stereocenter at C(11, variecolin numbering) was installed smoothly; initial kinetic deprotonation with KDA in the presence of the requisite additive HMPA and alkylation of the ensuing enolate with the bifunctional vinyl iodide[394] followed by methylation provided after iododestannylation the necessary cyclization precursor **5.21**. Treating vinyl iodide **5.21** with *n*-BuLi furnished rapid cyclization to afford a cycloheptene which upon oxidative rearrangement with PCC[395,396] provided the desired cycloheptenone **5.22** in moderate yield. This cycloheptenone **5.22** served as precursor to the central eight-membered B-ring, the hallmark of the variecolin sesterterpenoids.



Scheme 5.4 Ring expansion providing the central eight-membered B-ring.

Reduction of heptenone **5.22** under Birch-type conditions followed by PCC oxidation provided an inseparable 2.2:1.0 mixture of ketone products **5.23** and **5.24** (Scheme 5.4). Ketone **5.23** was transposed into **5.25** in 44% yield through a four step sequence. Cycloheptanone **5.25** was poised to undergo a four-step ring-expansion sequence to furnish the central B-ring. When cycloheptanone **5.25** was treated with KHMDS and the resulting enolate trapped with TMSCl, a regioisomeric mixture of silyl enol ethers was obtained. This material was subjected to dioxygen-accelerated cyclopropanation conditions,[397] and the ensuing silyl cyclopropyl ethers were treated with iron(III) chloride to give a mixture of β-chloro-ketones. Next, the mixture was reacted with NaOAc to afford two regioisomeric ketoenones in a combined 86% yield of which the desired cyclooctenone **5.26** was attained as the major product in 64% yield over the four step sequence.

With the BCD-ring system in place, cyclooctenone **5.26** was ready to undergo a methylenecyclopentane annulation forming the A ring (Scheme 5.5). In the event, Lewis-acid-accelerated conjugate addition of a bifunctional homocuprate to cyclooctenone **5.26** followed by a Finkelstein reaction to afford a more reactive alkyl iodide and lithium *tert*-butoxide-mediated alkylation gave exclusively the desired *cis*-fused 5,8-ring system **5.27** in 53% yield for this three step sequence. Installation of C(20) was achieved by kinetic deprotonation of ketone **5.27** and subsequent trapping of the enolate with *N*-phenyltrifluoromethanesulfonimide to provide the corresponding triflate. This material was subjected to palladium-catalyzed carbonylation conditions affording ester **5.28** in good yield. After extensive experimentation, a crucial catalytic hydrogenation protocol for chemo- and diastereoselectively reducing the exocyclic methylene double bond in the presence of the isopropenyl moiety was discovered. Catalytic hydrogenation using 5% platinum on alumina followed by DIBAL reduction afforded allylic alcohol **5.29** as a single diastereomer in excellent yield.



Scheme 5.5 End-game for Walker's and Piers' approach.

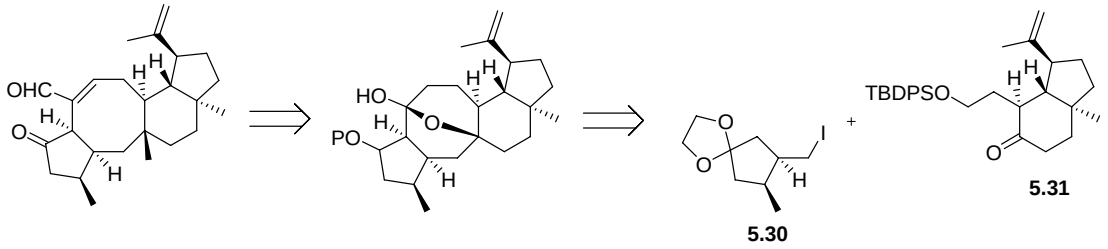
From the central allylic alcohol **5.29** several analogs of variecolin (**5.1**) could be synthesized with relative ease. Manganese dioxide oxidation of allylic alcohol **5.29** provided (±)-5-deoxyvariecolin (**5.15**) in good yield. (±)-5-deoxyvaricolol (**5.16**) could be attained from the same intermediate **5.29** via a two step sequence. The addition of $Pb(OAc)_4$ in the presence of $CaCO_3$ afforded (±)-5-deoxyvariecolol (**5.16**) and (±)-5-deoxyvariecolin (**5.15**) in a 2:3 ratio. Upon treatment with $NaBH_4$ (±)-5-deoxyvariecolin (**5.15**) was reduced to allylic alcohol **5.29** (58% yield) allowing for recycling, while (±)-5-deoxyvariecolol (**5.16**) could be isolated in 39% yield. The formation of the cyclic ether moiety in **5.16** probably proceeds via formation of an alkoxy radical formed through homolytic decomposition of an intermediate lead(IV) alkoxide, internal 1,5-hydrogen transfer to yield a C-5 radical, and final ether ring closure.[398] The cyclic ether was oxidized using Collins' reagent providing (±)-5-deoxyvariecolactone (**5.17**) in excellent yield.

In summary, Piers have provided access to the variecolin analogs (±)-5-deoxyvariecolin (**5.15**), (±)-5-deoxyvariecolol (**5.16**), and (±)-5-deoxyvariecolactone (**5.17**) in a racemic manner employing a highly linear sequence. The longest linear sequence contains 28 steps providing (±)-5-

deoxyvariecolactone (**5.17**) in an overall 1.0% yield. Unfortunately, the synthesis is marred by several inefficient steps which can be ascribed to selectivity issues and furthermore, the ring-expansion to build the requisite eight-membered ring takes eleven steps from the seven-membered ring precursor. To complete the racemic synthesis and access the variecolin family all that remains is oxidation of C(5) to attain the correct oxidation state.

5.2.2 Molander's Samarium(II) Iodide-Mediated Annulation Approach

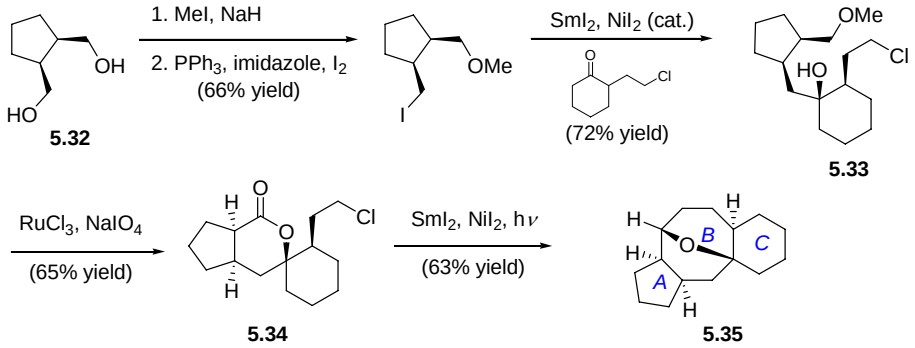
The first enantioselective approach toward the total synthesis of variecolin (**5.1**) was reported by Molander and co-workers in 2001.[399] This first generation approach was based on Hensens original assignment founded on biosynthetic consideration, hence the synthesis targeted *ent*-variecolin (**5.2**) while the second generation approach was based on the revised structure (cf. Figure 5.1).[400] The central design feature in both approaches was to construct the eight-membered B-ring employing a samarium(II) iodide-mediated coupling-annulation sequence of an alkyl iodide **5.30** and bicyclic ketone **5.31** (Scheme 5.6). This strategy had previously been used by Molander to forge medium sized carbocycles.[401,402]



Scheme 5.6 Molander's convergent approach to variecolin (**5.1**).

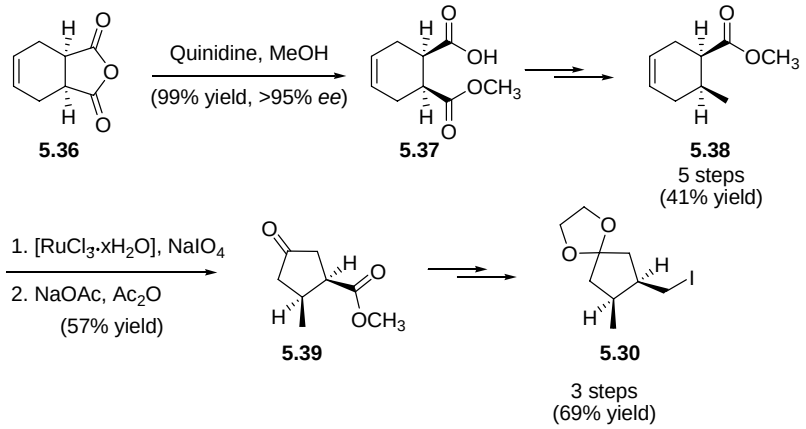
The most important lesson from Molander's first generation approach was provided by model studies on the sequenced samarium(II) iodide coupling-annulation (Scheme 5.7). These studies revealed that the sequenced coupling had to be performed in two separate steps. In the event, diol **5.32** was converted into chloride **5.33** utilizing standard chemistry followed by a samarium(II) iodide-mediated coupling. Chloride **5.33** was obtained as a 1:1 diastereomeric mixture due to the employment of racemic material and the addition to the ketone occurring *trans* addition to the alkyl chloride side-chain. Employing a protocol developed by Sharpless,[403] methyl ether **5.33** was oxidized using a catalytic amount of ruthenium tetraoxide generated *in situ* from ruthenium(III) chloride and sodium periodate which provided lactone **5.34** directly. When lactone **5.34** was exposed to samarium(II) iodide under photochemical conditions, the prerequisite hemiketal **5.35** was

attained in good yield providing important proof-of-principle for the potential utility of the this strategy in constructing the central ABC ring-system of variecolin (**5.1**).



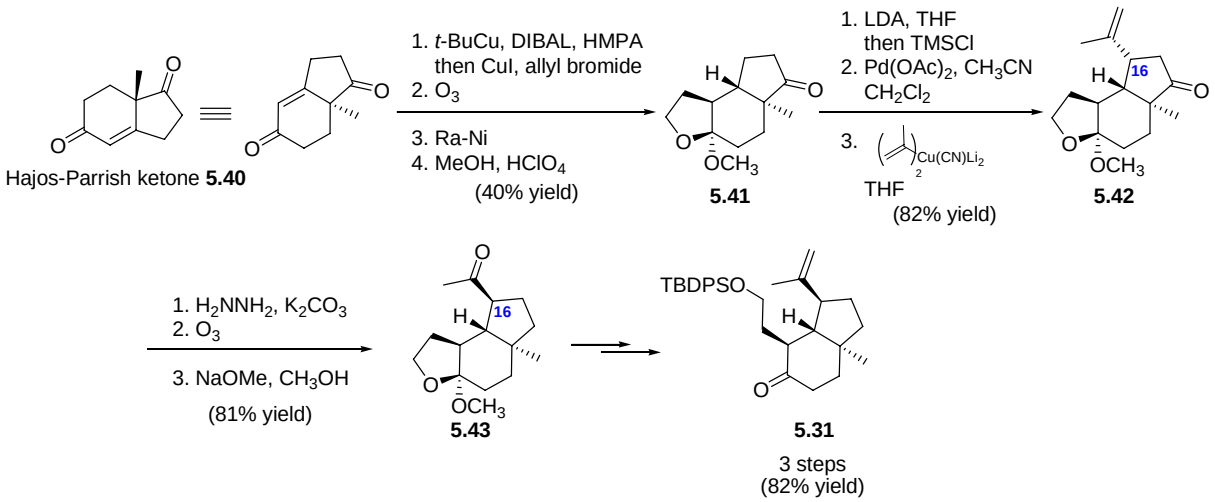
Scheme 5.7 Model studies on the key samarium(II) iodide-mediate sequence.

With this important knowledge in mind, Molander and co-workers embarked on the second generation approach toward variecolin (**5.1**). The initial focus was to devise efficient routes that would allow for asymmetric synthesis of the two coupling partners alkyl iodide **5.30** and ketone **5.31**. The preparation of alkyl iodide **5.30** commenced from prochiral *meso*-anhydride **5.36** which after subjection to desymmetrization conditions developed by Bolm and co-workers[404] afforded monoester **5.37** in virtually quantitative yield and high *ee* (Scheme 5.8). A series of functional group manipulations furnished ester **5.38** which upon oxidative cleavage and decarboxylative cyclization provided cyclopentanone **5.39**. Further standard transformations gave the requisite alkyl iodide coupling partner.



Scheme 5.8 Asymmetric synthesis of alkyl iodide **5.30**.

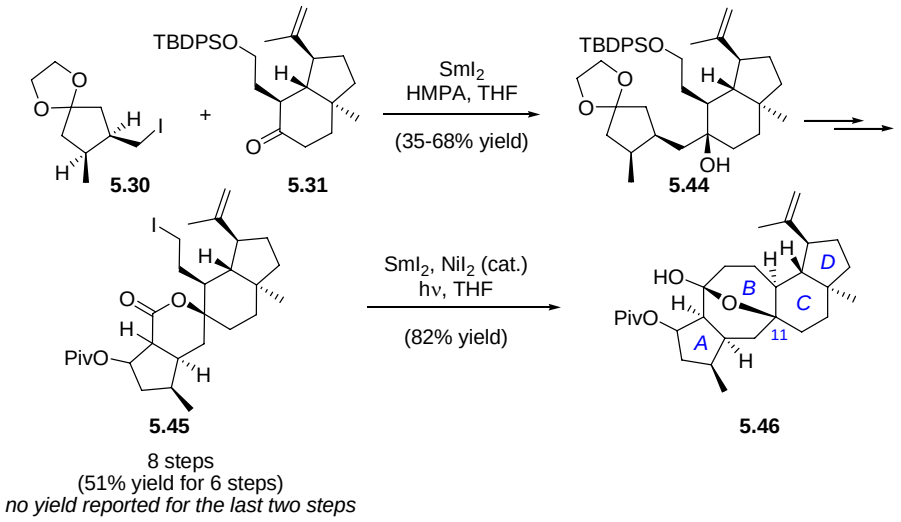
The correct stereochemistry for the bicyclic ketone coupling partner **5.31** was attained from Hajos-Parrish ketone **5.40** (Scheme 5.9).[405,406] The overarching strategy was that the all-carbon quaternary stereocenter in the Hajos-Parrish ketone would allow for the diastereoselective formation of the remaining stereocenters in the coupling partner **5.31**. Ketone **5.40** was reduced with DIBAL-HMPA in the presence of *tert*-butyl cuprate, and the ensuing aluminium enolate was trapped with allyl bromide. Ozonolysis of this material followed by selective Raney-Ni reduction and acetal formation afforded methyl ether ketal **5.41** in moderate yield for this four-step sequence. Unfortunately, a sequence consisting of a two-step Saegusa-oxidation[407] and cuprate addition gave the wrong stereochemistry at C(16) providing the undesired diastereomer **5.42**. However, this could relatively easily be resolved through Wolff-Kishner reduction, ozonolysis and epimerization in the presence of NaOMe. Finally, acetal **5.43** was transformed into the required fragment **5.31** through a series of standard manipulations.



Scheme 5.9 Synthesis of bicyclic ketone **5.31** commencing from Hajos-Parrish ketone **5.40**.

With access to enantiomerically pure coupling partners Molander and co-workers focused on the samarium(II) iodide-mediated Barbier-type coupling of fragment **5.31** and **5.30**. Extensive experimentations revealed that HMPA was crucial in order to obtain moderate yields of the coupling product **5.44** (Scheme 5.10). It is well known that HMPA accelerates these Barbier-type couplings. This effect is ascribed to an increase in the reduction potential of samarium(II) iodide when coordinated to a Lewis basic co-solvent.[408] The exact nature of the active species is still a subject of debate: in the presence of four equivalents of HMPA, Flowers and co-workers[409,410] suggest an uncharged complex [$SmI_2(HMPA)_4$], while Skrydstrup and co-workers[411,412] have provided

evidence for an ionic cluster $[Sm(HMPA)_4(THF)_2]^{2+}$ 2 I^-. From the tertiary alcohol **5.44** it took eight steps to arrive at the spirocyclic lactone **5.45**. Gratifyingly, when the conditions developed for the model system were implemented, the hemiketal **5.46** containing the 5,8,6,5-tetracyclic system of variecolin (**5.1**) was obtained in 82% yield, however, due to several low-yielding steps *en route* to spirolactone **5.45** material constraints precluded further studies toward the total synthesis of variecolin (**5.1**).



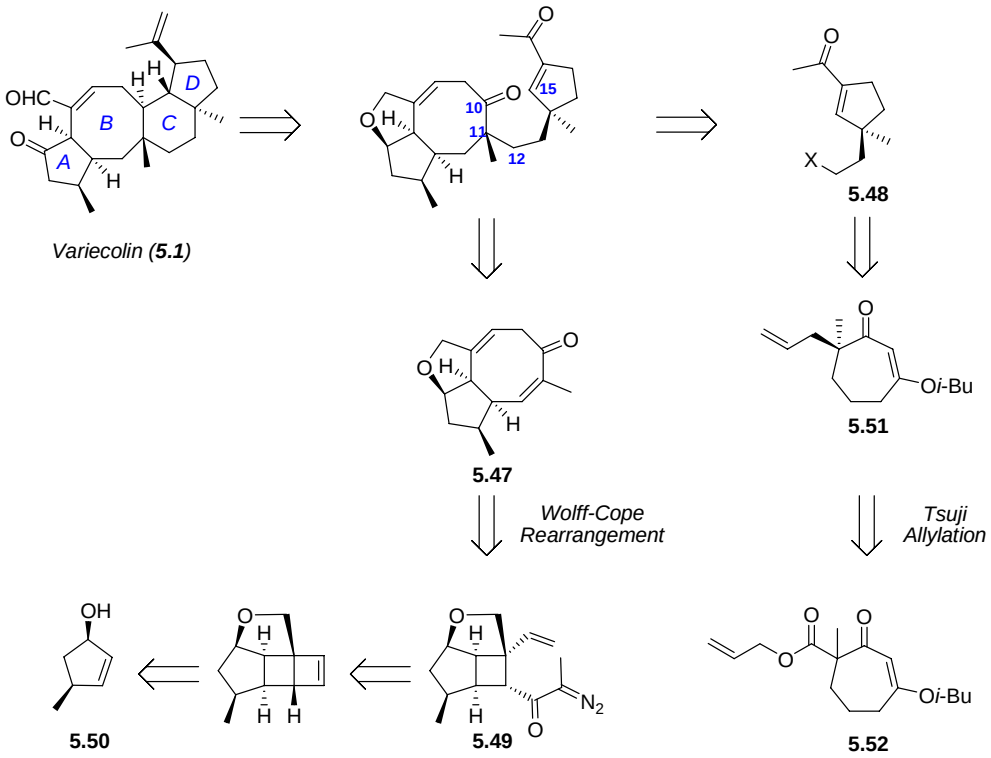
Scheme 5.10 Molander's construction of the ABCD ring system.

In summary, Molander and co-workers have demonstrated the utility of samarium(II)-iodide-mediated Barbier-type alkylation and annulation in the construction of the core skeleton of variecolin. Compared to Piers' approach, Molander has achieved higher efficiency through a convergent synthetic strategy. Although the fragments **5.30** and **5.31** have been prepared in enantiomerically pure form, their synthesis still leaves room for improvement (11 steps to fragment **5.30** 16% overall yield, 13 steps to fragment **5.31** 22% overall yield). Moreover, the synthesis of spirolactone **5.45** is hampered by several low-yielding steps, and perhaps most importantly, all attempts to install the C(11) quaternary stereocenter at a late stage in the synthesis have failed, which may call for a revised strategy confronting this problem at an earlier stage.

5.3 Retrosynthetic Analysis and Synthetic Design

Our efforts toward the synthesis of this intriguing family of sesterterpenoids was concentrated around variecolin (**5.1**), since it has a highly interesting biological profile, and furthermore, retains

the major structural challenges presented by this class of natural products. Therefore, it was anticipated that an efficient synthesis of variecolin would provide access to the remaining family members. With a novel tetracyclic ring system featuring a central eight-membered ring, eight stereogenic centers two of which are all-carbon quaternary, an AB *cis* ring fusion, BC and CD *trans* ring fusions, variecolin (**5.1**) is a topographically complex target molecule (Scheme 5.11). Additionally, the relatively low degree of oxidation of the central ring system poses a significant challenge in devising a synthetic strategy due to the scarcity of functional group handles.



Scheme 5.11 Retrosynthetic analysis of variecolin (**5.1**).

The overarching strategy was to utilize the structural challenges presented by variecolin (**5.1**) to expand the boundaries of synthetic methodologies recently developed in the Stoltz laboratory.[413-415] A central design feature was to convergently unite an AB fragment **5.47** and a D-ring fragment **5.48** through a two-carbon tether and subsequently forge the B-ring by way of reductive cyclization. We envisioned cleavage of the tetracyclic structure by scission of the C(10)-C(15) bond employing an intramolecular conjugate radical addition of the AB-ring into the D-ring enone. Disconnection of the C(11)-C(12) bond through reductive coupling would provide the AB-ring fragment **5.47** and the D-ring precursor **5.48**. We anticipated that the AB-ring fragment would be available from a Wolff-

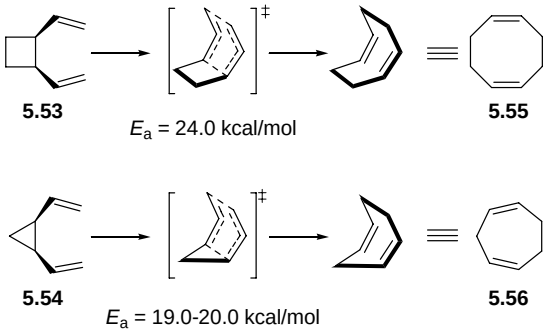
Cope rearrangement of the densely functionalized cyclobutane **5.49** which in turn could be derived from allylic alcohol **5.50** employing a tethered cycloaddition. Acyclcyclopentene **5.48** could arise from ring-contraction of vinylogous ester **5.51**, ultimately accessible from β-ketoester **5.52** utilizing asymmetric decarboxylative allylation.

5.4 A Tandem Wolff–Cope Based Approach Toward the AB-Ring System

The unique structural features of eight-membered cycloalkanes have spurred much research to uncover conformational preferences, strain, and transannular interactions.[416] Although eight-membered rings are less common in nature than five- and six-membered rings, they still have a high prevalence among natural products.[416] The synthesis of eight-membered carbocycles has been a long-standing problem since extrapolation of existing protocols for ring formation has proved difficult. Cyclization of acyclic precursors to construct eight-membered rings is disfavored by a high degree of ring strain and transannular interactions.[417] Hence until the onset of the 1980s relatively few methods to synthesize eight-membered ring had been disclosed. However, the isolation of a variety of complex natural products containing this intriguing structural moiety have spurred great progress in synthetic methodology to assemble eight-membered rings since then.[417,418] A prominent example that has impelled a tremendous amount of research is the anticancer agent paclitaxel (Taxol).[419,420] Despite notable breakthroughs, the selective formation and functionalization of eight-membered rings remain a significant challenge and an active research field.[421-425]

5.4.1 Background for the Wolff-Cope Rearrangement

A versatile and effective method for constructing functionalized seven- and eight-membered carbocycles is the ring-expansion of *cis*-1,2-divinylcyclobutanes and *cis*-1,2-divinyl-cyclopropanes via [3,3]-sigmatropic Cope rearrangements (Scheme 5.12). Starting around 1980, these rearrangements have proved a rapid and reliable route particularly to eight-membered carbocycles and have found widespread use in total synthesis.[426] The thermal rearrangements of divinylcyclobutane **5.53** and divinylcyclopropane **5.54** were first reported by Vogel in 1958[427] and 1960,[428] respectively.

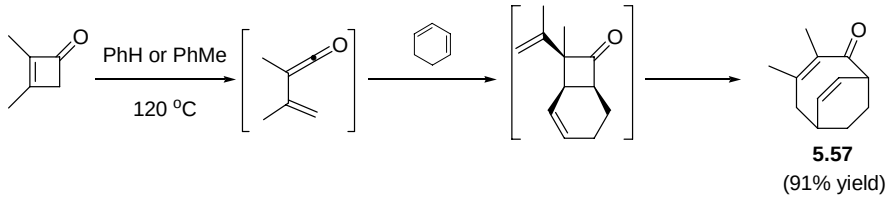


Scheme 5.12 Strain-releasing Cope rearrangement.

The mechanism of the Cope rearrangement has been subject to thorough investigations. Two concerted aromatic transition states are now broadly accepted for the parent 1,5-hexadiene namely: a chair-like transition state and a boat-like transition state. For the majority of 1,5-hexadienes the chair-like reaction path is dominant.[429,430] In the cases of *cis*-divinylcyclobutane and *cis*-divinylcyclopropane, however, it is widely believed that the rearrangement predominantly proceeds in a concerted fashion via boat-like transition states where the vinyl groups are situated above the cyclobutane and cylopropane ring in an *endo* fashion (Scheme 5.12).[431-437] Based on kinetic measurements, DeBoer[438] found that the activation energy E_a for the rearrangement of **5.53** into **5.55** is 24.0 kcal/mol, which has recently been supported by theoretical studies by Ozkan and Zora.[439] Notably, Schneider and Rau discovered that the E_a for the rearrangement of **5.54** into **5.56** is approximately 4.0-5.0 kcal/mol lower *i.e.* 19.0-20.0 kcal/mol.[440] This difference in E_a is further reflected in the difficulties encountered in trying to prepare **5.54** synthetically. It took thirteen years from Vogel's original disclosure of this transformation until Brown and co-workers[441] successfully prepared and isolated **5.54**. Hence, the strain-releasing driven Cope rearrangement of **5.54** is proceeding at much lower reaction temperatures than the Cope rearrangement of **5.53**. *cis*-Divinylcyclopropane **5.54** has been shown to rearrange into **5.56** with a half-life of approximately 90 s at 35 °C.[441]

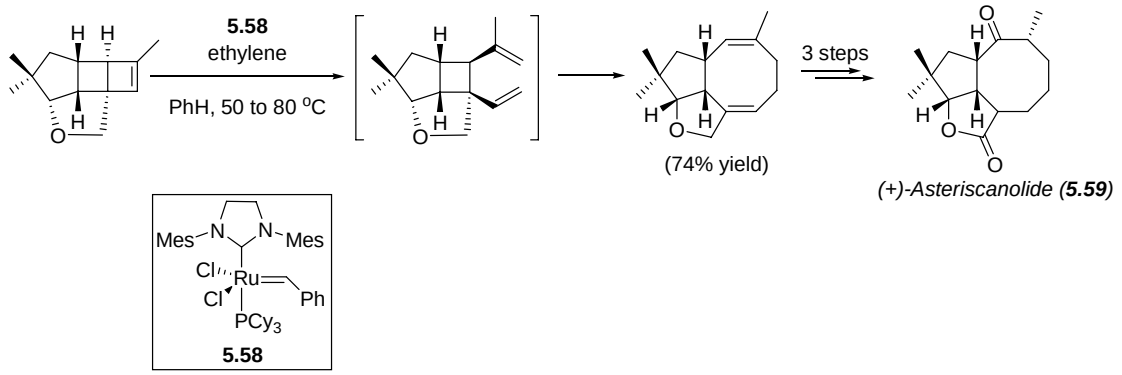
An early example exploring this type of transformation to prepare cyclooctaenones was disclosed by Danheiser.[442] Creatively, Danheiser and co-workers used an electrocyclic ring-opening of a cyclobutenone to generate a vinylketene derivative that via a [2 + 2] cycloaddition provided a *cis*-

divinyl cyclobutane (Scheme 5.13). At elevated reaction temperatures this intermediate underwent a Cope rearrangement furnishing **5.57** containing an eight-membered ring.[a]



Scheme 5.13 Danheiser's formal [4 + 4] approach to cyclooctaenones.

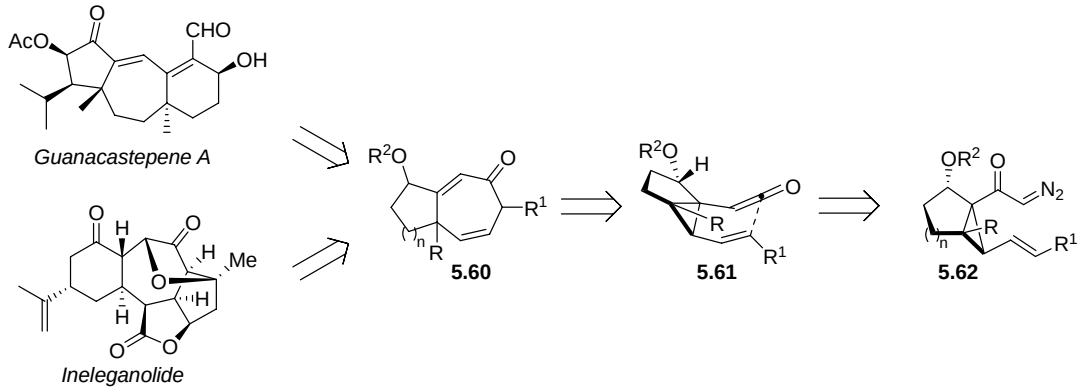
Recently, Snapper[443] described an elegant cascade, which provide a concise entry into [5-8] fused ring systems. Ring-opening cross-metathesis afforded access to densely functionalized *cis*-vinylcyclobutane derivatives readily undergoing a strain-releasing Cope rearrangement upon heating. Moreover, this methodology was implemented at key steps in the total synthesis of (+)-asteriscanolide (**5.59**) by Limanto and Snapper in 2000 (Scheme 5.14).[444]



Scheme 5.14 Snapper's approach to (+)-asteriscanolide (**5.59**).

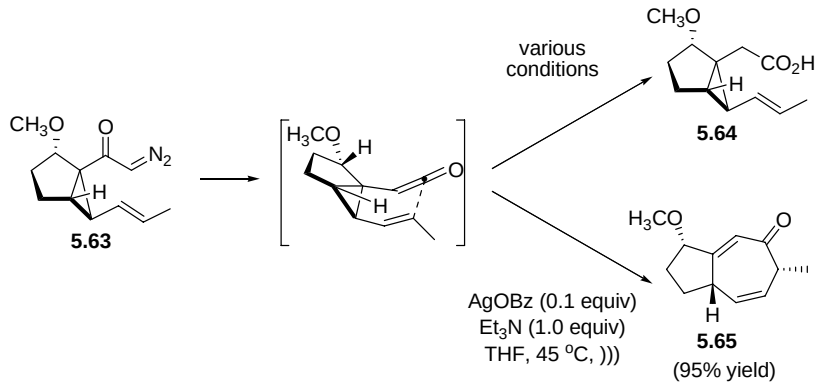
In 2003, Stoltz and co-workers[413,445] realized the potential of combining the Wolff rearrangement and the strain-releasing Cope rearrangement of *cis*-vinylcyclopropane-type systems in tandem (Scheme 5.15). This interest was propelled by synthetic efforts toward guanacastepene A[446-448] and ineleganolide.[449] The requisite cycloheptadienone **5.60** was envisioned to arise from a ketene-Cope rearrangement with simultaneous opening of a cyclopropane ring. Ketene **5.61** could stem from diazoketone **5.62** through a Wolff rearrangement.

[a] Interestingly, the three major classes of pericyclic reactions (electrocyclic ring-opening, cycloaddition, and sigmatropic rearrangement) are combined in this protocol.



Scheme 5.15 The Wolff-Cope rearrangement approach to fused [5-7] systems.

The Wolff rearrangement was first disclosed in 1902.[450] Since the initial discovery the rearrangement has been studied in detail, and this has revealed numerous protocols facilitating the transformation both under photolytic and thermolytic conditions. Accordingly, α-diazoketone **5.63** was prepared and subjected to a range of conditions including thermolysis in the presence of promoters such as Ag_2O, AgOBz, CuI, and Cu(0).[451-453] While the exploratory studies were met with limited success, a key finding from these investigations was that the homologated acid **5.64** was produced as one of the byproducts indicating that formation of the desired ketene was taking place while the ketene vinyl cyclopropane Cope rearrangement was not occurring (Scheme 5.16).

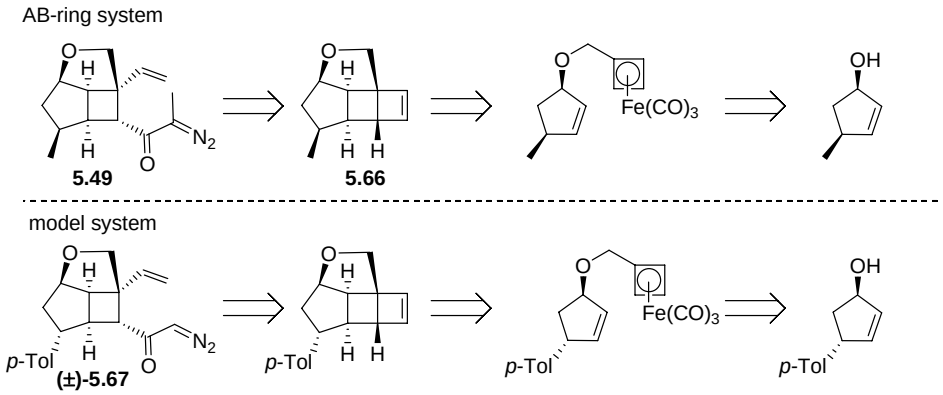


Scheme 5.16 Tandem Wolff-Cope rearrangement.

After extensive experimentation, Stoltz and co-workers decided to employ sonochemical conditions originally disclosed by Montero[454] for the Wolff rearrangement. These conditions afforded the desired Wolff-Cope rearrangement product **5.65** in 95% isolated yield. This silver-catalyzed process constitutes a mild protocol allowing for rapid access to highly functionalized fused [5-7] and [6-7] ring systems.

5.4.2 Retrosynthesis of the AB-Ring Fragment

In order to probe the feasibility of the key Wolff-Cope rearrangement, we had to devise a stereoselective synthesis of a highly functionalized cyclobutene system. To this end we sought to implement an intramolecular cycloaddition between cyclobutadiene and an unactivated alkene (Scheme 5.17). Furthermore, it was envisioned that the alkene moiety of cyclobutene **5.66** could be regioselectively cleaved utilizing termini differentiating ozonolysis and ultimately provide access to Wolff-Cope substrate **5.49**. We decided to devise a model system **5.67** to investigate the viability of the synthetic route leading to Wolff-Cope substrate **5.49** as well as to explore the possibility of telescoping the Wolff-Cope methodology to the synthesis of eight-membered rings. It was anticipated that this model system would retain most of the synthetic challenges presented by the real system, and that most of the intelligence gathered from these endeavors could be transferred to our total synthesis of variecolin.

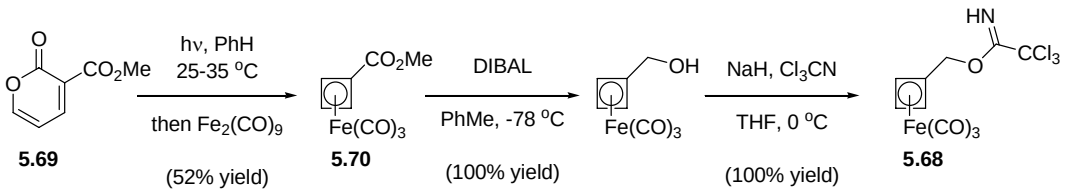


Scheme 5.17 Retrosynthesis of the AB-fragment and the AB-fragment model.

5.4.3 Model Studies on the Wolff-Cope Rearrangement Toward the AB-Ring System[a]

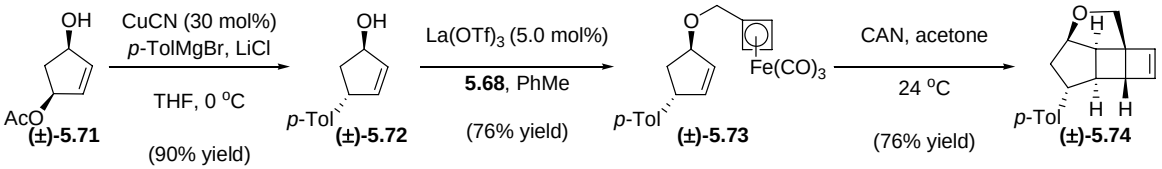
Our synthetic efforts necessitated the synthesis of an appropriate cyclobutadiene-iron species that would allow for efficient alcohol alkylation. To this end we decided to target trichloroacetimidate **5.68** (Scheme 5.18). We commenced from pyrone **5.69** which have previously been reported by Corey and Watt.[455] Pyrone **5.69** was transformed into cyclobutadiene-iron complex **5.70** utilizing known methods.[444] Reduction with DIBAL followed by treatment with sodium hydride and trapping with trichloroacetonitrile afforded trichloroacetimidate **5.68** in quantitative yield.

[a] The work described in chapter 5.4.3 was primarily performed by Ph.D. student Michael R. Krout, hence no experimental details will be provided.



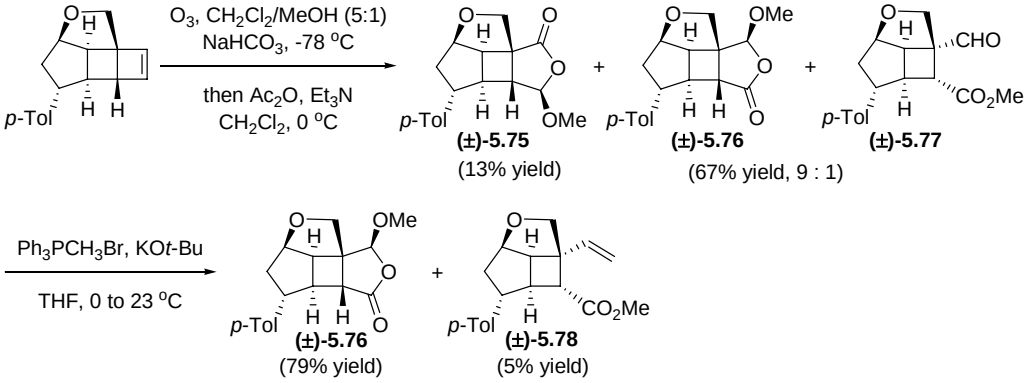
Scheme 5.18 Synthesis of trichloroacetimidate **5.68**.

A copper(I)-catalyzed S_N2 displacement of monoacetate **(±)-5.71** with *p*-tolylmagnesium bromide smoothly afforded allylic alcohol **(±)-5.72** (Scheme 5.19).[456] The cycloaddition substrate **5.73** was attained in good yield through a lanthanum(III) triflate-catalyzed alkylation with trichloroacetimidate **5.68**.[457] Inspired by oxidative unmasking conditions previously employed by Snapper,[458] we subjected **(±)-5.73** to ceric ammonium nitrate which facilitated liberation of cyclobutadiene, that immediately underwent an intramolecular cycloaddition to provide the desired cyclobutene **(±)-5.74** in good yield. Since the only observable product is the cycloadduct **(±)-5.74**, a concerted mechanism appears to be operative, which is in accordance with previous mechanistic investigations conducted by Houk and Snapper.[459] This type of transformation was first reported by Grubbs[460] employing tethered alkynes and has later been widely expanded by Snapper and co-workers.[443,444,458,461,462]



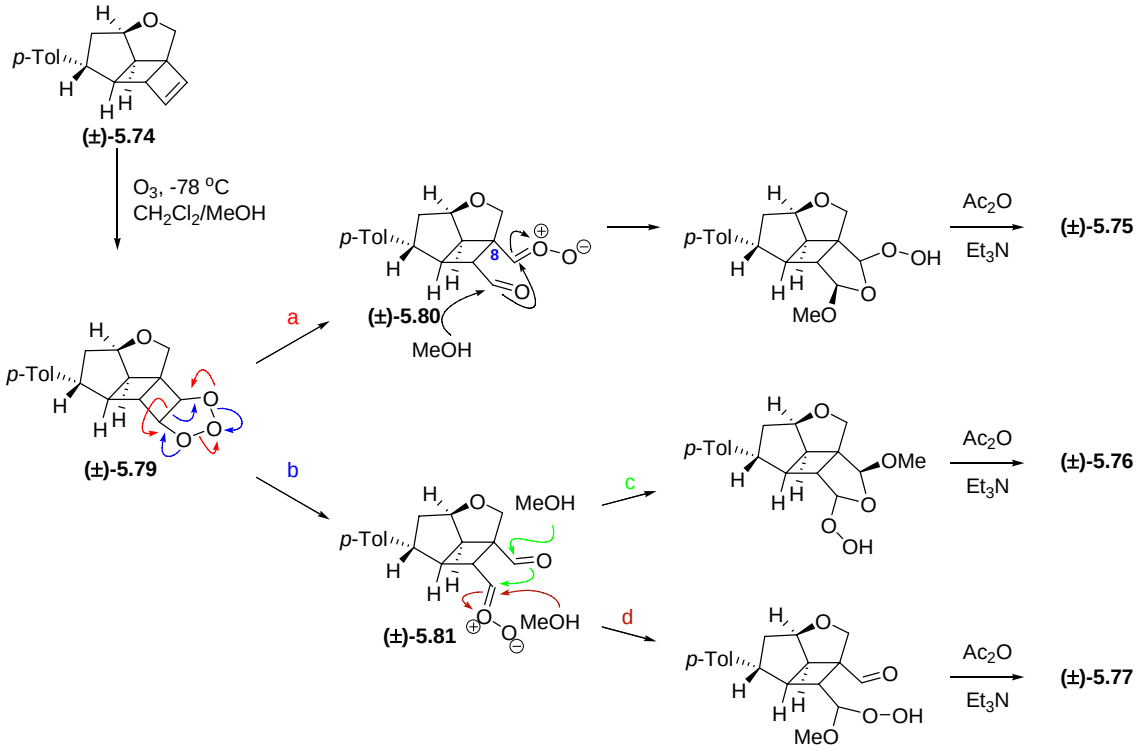
Scheme 5.19 Intramolecular cycloaddition affording cyclobutene **5.74**.

Having established an efficient procedure for preparing cyclobutene **5.74** our focus shifted toward regioselective functionalization of the olefin moiety. Faced with this challenge, we decided to explore a termini differentiating ozonolysis first reported by Schreiber and co-workers.[463] Subjecting cyclobutene **5.74** to typical conditions *i.e.* ozonolysis in $NaHCO_3$-buffered CH_2Cl_2/MeOH followed by dehydration with acetic anhydride and triethylamine furnished a mixture of compounds consisting of acetal **5.75** and an inseparable mixture of acetal **5.76** and aldehyde **5.77** (Scheme 5.20). The mixture of **5.76** and **5.77** was employed directly in a Wittig methylenation, which provided acetal **5.76** as the major product along with minor amounts of the desired alkene **5.78**.



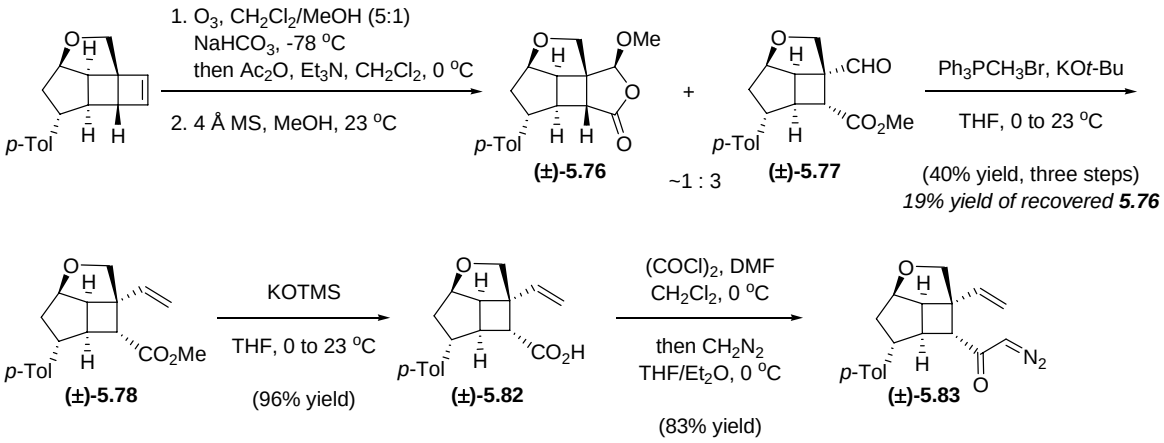
Scheme 5.20 Termini differentiating ozonolysis.

The formation of regioisomeric acetals **5.75** and **5.76** can be explained by two diverging fragmentation pathways (Scheme 5.21 pathway *a* and *b*) from the intermediate primary ozonide **5.79**. Breakdown of ozonide **5.79** via retro [2 + 3] cycloaddition along pathway *a* would locate the carbonyl oxide on the more hindered carbon C(8) (**5.80**), and subsequent nucleophilic attack by methanol followed by dehydration generates acetal **5.75**. Fragmentation via pathway *b* would generate carbonyl oxide **5.81** which in turn can follow two different reaction pathways. Reaction with methanol through path *c* would after dehydration afford acetal **5.76**, whereas initial attack on the carbonyl oxide moiety via path *d* ensued by dehydration generates the desired aldehyde **5.77**. Despite the desired aldehyde **5.77** being the minor product of this reaction the, required reaction pathway *b* is favored in ~3:1 ratio which can possibly be explained by the sterics of cyclobutene **5.74**.



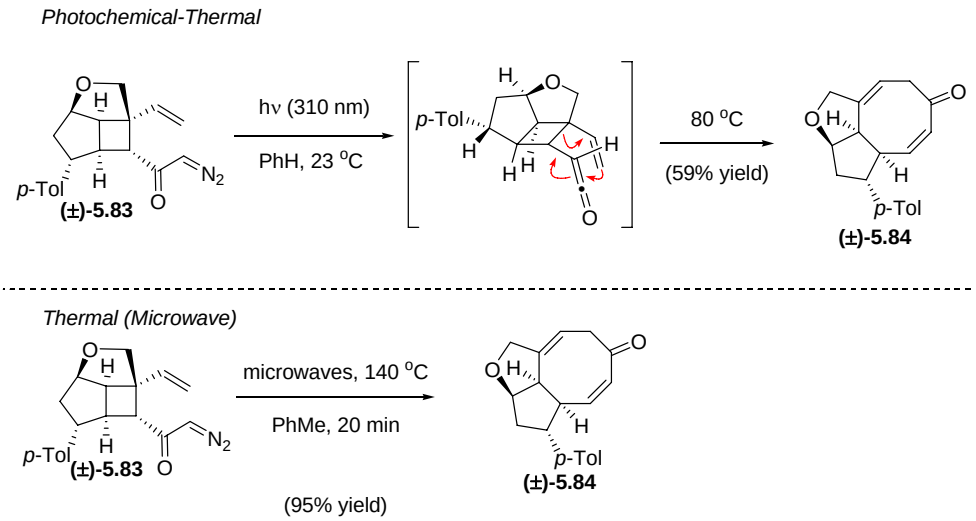
Scheme 5.21 Mechanistic rationale for the ozonolysis of cyclobutene **5.74**.

The fact that aldehyde **5.77** was formed as the minor component in the ozonolysis was detrimental to our progress toward a Wolff-Cope substrate. However, owing to the isomeric relationship of acetal **5.76** and aldehyde **5.77**, we reasoned that these species could be equilibrated. It was found that treating acetal **5.76** and aldehyde **5.77** with 4 Å molecular sieves shifted the equilibrium in favor of the aldehyde (**5.76**:**5.77** ~ 1:3) (Scheme 5.22). The predominant formation of acetal **5.76** over aldehyde **5.77** during the ozonolysis is most likely a result of the close proximity of the carbonyl and the carbonyl oxide moieties on the cyclobutane ring. Moreover, from these results it is evident that acetal **5.76** constitutes the kinetic product while aldehyde **5.77** is the thermodynamically favored. The mixture of acetal **5.76** and aldehyde **5.77** was treated with methyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF affording the desired alkene **5.78** in 40% yield over three steps along with 19% yield of acetal **5.76** which allowed for recycling of material through equilibration. Alkene **5.78** was treated with potassium trimethylsilanolate[464] to afford the corresponding acid **5.82** which was transformed into α-diazoketone **5.83** through the acid chloride and reaction with diazomethane under standard conditions.



Scheme 5.22 Synthesis of α-diazoketone **5.83**.

With α-diazoketone **5.83** in hand, we commenced studies on the crucial tandem Wolff-Cope rearrangement which ultimately would provide access to the eight-membered B-ring of variecolin (**5.1**, Scheme 5.23). Initial experiments revealed that the previously reported[413] silver(I)-catalyzed sonochemical or photochemical reactions conditions were unsuitable for mediating the requisite Wolff-Cope rearrangement. A control experiment conducted in methanol clearly revealed that the photochemically induced Wolff rearrangement was rapidly taking place at room temperature since the intermediate ketene could be trapped as the corresponding Arndt-Eistert homologated ester in high yield. As discussed previously (cf. chapter 5.4.1), the Cope rearrangement of *cis*-divinylcyclopropanes in general occurs at a much lower temperature than the corresponding rearrangement of *cis*-divinylcyclobutanes. This led us to investigate photochemical conditions for the initial Wolff rearrangement followed by thermolysis of the putative intermediate ketene. To our delight, cyclooctenone **5.84** was obtained in 59% yield when diazoketone **5.83** was subjected to 310 nm light at room temperature followed by thermolysis at 80 °C. The stereochemical relationship in the product **5.84** can be accounted for by a boat-shaped transition state. The moderate yield could possibly be ascribed to the reactivity of the intermediate ketene and the time between photolysis and thermolysis. In order to address this problem we turned toward microwave conditions to promote the Wolff rearrangement[465] with the hope that the heat developed during irradiation also would facilitate the Cope rearrangement. Gratifyingly, the requisite cyclooctene **5.84** was attained very cleanly in an excellent 95% yield.



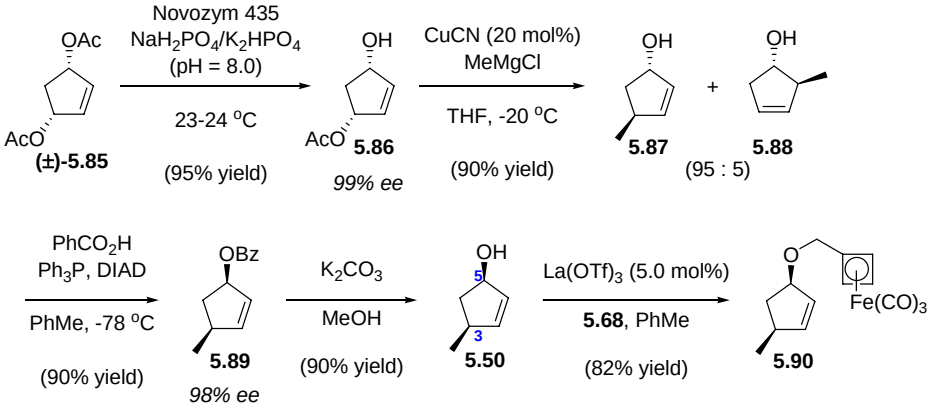
Scheme 5.23 Wolff-Cope rearrangement affording cyclooctene **5.84**.

In conclusion, these model studies have firmly established that the Wolff-Cope rearrangement strategy should be applicable to the synthesis of the core B-ring of variecolin, and furthermore, these studies have unraveled a novel means to forge eight-membered rings in synthesis.

5.4.4 Asymmetric Synthesis of the AB-Ring Fragment[a]

The asymmetric synthesis of the AB fragment required access to alcohol **5.50** in enantiopure form. We decided to commence from readily available *meso*-diacetate[466] **5.85** employing an enzyme-catalyzed desymmetrization (Scheme 5.24).[467] In the event, treating **5.85** with Novozym 435 under buffered conditions afforded the monoester **5.86** in excellent yield and 99% *ee*. A copper(I) cyanide-catalyzed S_N2 displacement of monoester **5.86** provided a mixture of alcohols **5.87** and **5.88** (95:5). This mixture was treated with benzoic acid, triphenylphosphine and DIAD to facilitate a Mitsunobu inversion furnishing the allylic benzoate **5.89** with the requisite *syn* relationship between C(3) and C(5).[456] Methanolysis of ester **5.89** followed by lanthanum(III)-catalyzed coupling with the cyclobutadiene-iron derivative **5.68** furnished the prerequisite intramolecular cycloaddition substrate **5.90**.

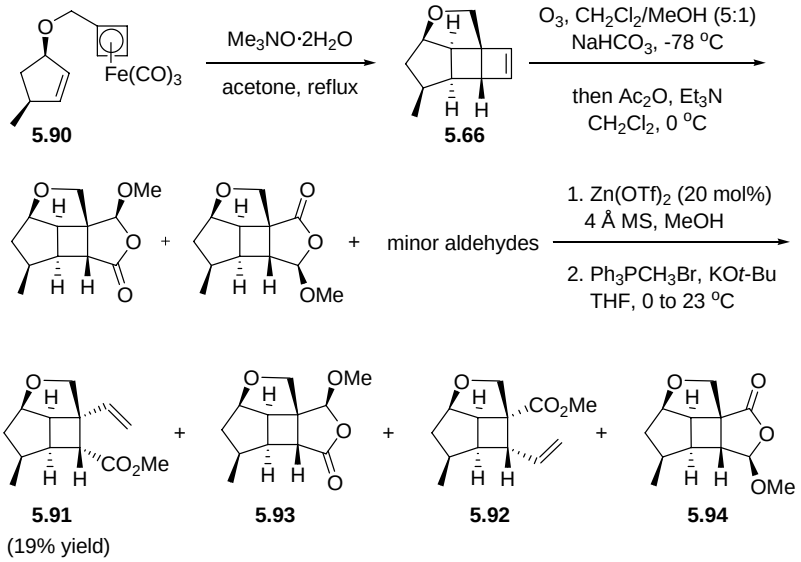
[a] The work described in chapter 5.4.4 was primarily performed by Ph.D. student Michael R. Krout, hence no experimental details will be provided.



Scheme 5.24 Synthesis of cycloaddition precursor **5.90**.

In contrast to the model system (cf. Scheme 5.19), attempts to effect the intramolecular cycloaddition by treating **5.90** with ceric ammonium nitrate were met with limited success providing complex reaction mixtures. Presumably, this can be ascribed to increased steric hindrance in the transition state *en route* to the cycloadduct caused by the *syn*-relationship between the methyl group at C(3) and the tethered diene. The major competing reaction is likely to be intermolecular dimerization of cyclobutadiene, and therefore we decided to employ trimethylamine *N*-oxide which is known to provide a slower and more controlled release of cyclobutadiene compared to ceric ammonium nitrate.[459] In the event, treating alkene **5.90** with trimethylamine *N*-oxide in refluxing acetone cleanly afforded the desired cycloadduct **5.66** as judged by TLC (Scheme 5.25). However, the volatility of this cyclobutene led to low isolated yields. Hence, cyclobutene **5.66** was only semipurified[a] before being subjected to ozonolysis, acetal equilibration and Wittig methylenation providing olefins **5.91** and **5.92** along with acetals **5.93** and **5.94**. This unoptimzed four step reaction sequence provided the desired alkene **5.91** in 19 % yield.

[a] The compound was purified by silica-gel chromatography, however, in general the fractions containing the desired product was not concentrated down to get a yield.



Scheme 5.25 Synthesis of alkene **5.91**.

Moreover, acetal **5.93** was of sufficient crystallinity to enable X-ray analysis, providing conformation of the relative stereochemistry of this polycyclic fragment (Figure 5.3).

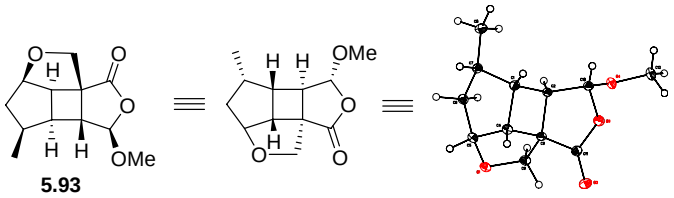
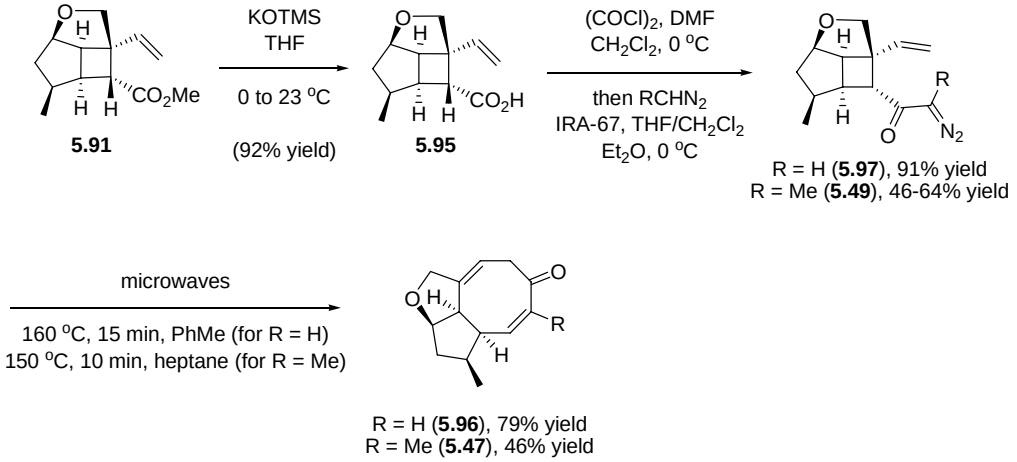


Figure 5.3 X-ray structure of acetal **5.93**.

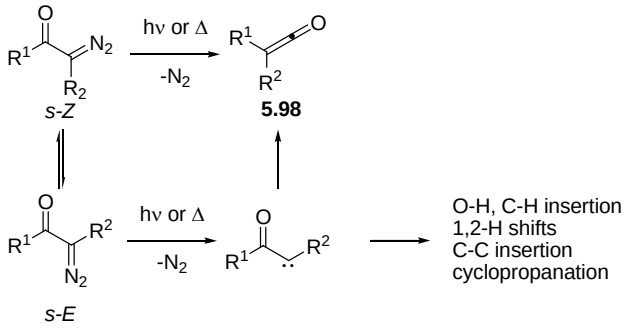
Alkene **5.91** was hydrolyzed using potassium trimethylsilanolate affording acid **5.95** in good yield (Scheme 5.26). Based on this intermediate, we decided to target two different AB-ring fragments **5.96** and **5.47**. The synthesis of α-diazoketone **5.97** was smoothly achieved by reacting acid **5.95** with oxalyl chloride in the presence of a catalytic amount of DMF followed by treatment with diazomethane. When subjected to our optimized Wolff-Cope conditions this α-diazoketone **5.97** afforded cyclooctene **5.96** cleanly in 79% yield. To access the AB fragment with a preinstalled methyl group at C(11, **5.47**), we employed diazoethane. Unfortunately, this procedure provided the corresponding α-diazoketone **5.49** in reduced yield, and all attempts to improve on this were unfruitful. The first attempt to convert α-diazoketone **5.49** into the requisite cyclooctene **5.47** implementing the microwave-mediated Wolff-Cope rearrangement gave **5.47** in a moderate 26%

yield along with multiple byproducts. In order to increase the yield, a range of different solvents were tested, and it was found that by switching to the less-polar solvent heptane, the desired cyclooctene **5.47** could be attained in 42% isolated yield.[a]



Scheme 5.26 Synthesis of the α-diazoketones and Wolff-Cope rearrangement.

A key observation from these experiments is the significant drop in the yield of the Wolff-Cope product when introducing an α-alkyl substituent. This reduced yield combined with the detection of multiple byproducts suggests that competing reaction pathways are functioning under the reactions conditions. The Wolff-rearrangement has been subject to thorough mechanistic investigations, and it is widely accepted that two different pathways contribute to the formation of ketene **5.98** (Scheme 5.27).[452,468,469] The ketene can be formed either via a concerted mechanism expelling nitrogen as the substituent R^1 migrates or through the intermediacy of an α-carbonyl carbene.



Scheme 5.27 Competing pathways of the Wolff-rearrangement.

[a] Ongoing efforts are directed toward improving the yield of this reaction as well as elucidating the structure of the major byproducts. One major byproduct seems to stem from intramolecular cyclopropanation *i.e.* carbene-like reactivity.

The factors governing whether the concerted path or the carbene path are operational are thus not completely understood. Nonetheless, it has been shown that the conformation of the O=C–C=N_2 group (*i.e.* s-*Z* versus s-*E*) has a significant influence on which pathway is dominating. Kaplan and co-workers[470-472] have previously shown that the *s-E* conformation favors the carbene pathway, and in the case of α-diazoketone **5.49**, the presence of an α-methyl group may enforce the adoption of an *s-E* conformation around the diazo-group, which could lead to carbene-like reactivity and in turn byproducts resulting from *e.g.* C-H insertion, 1,2-H shifts, and cyclopropanation. The mechanistic picture, however, is not clear-cut since some α-diazo ketones known to exist in the *s-E* conformation produce ketenes easily.[473]

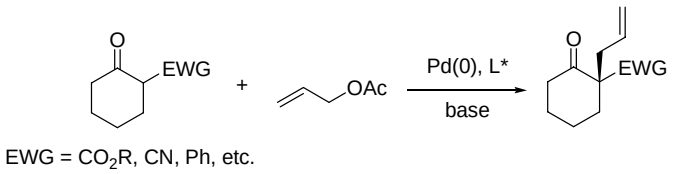
In summary, the successful synthesis of the AB-ring fragment has showcased the potential for utilizing the Wolff-Cope strategy in the construction of the central eight-membered ring of variecolin. Moreover this constitutes the first example of an α-substituted diazoketone undergoing the tandem Wolff-Cope rearrangement. In addition, this route will provide material to support our ongoing studies focusing on fragment coupling studies toward completing the total synthesis of variecolin.

5.5 Catalytic Asymmetric Synthesis of the D-ring Fragment

5.5.1 Background for the Tsuji Allylation

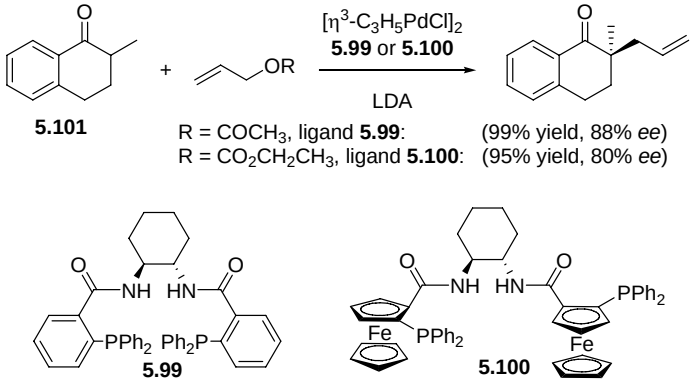
Quaternary stereocenters are ubiquitous in a wide variety of natural products with important structural and biological properties. As a result, the asymmetric catalytic construction of all-carbon quaternary stereocenters remains a significant challenge to synthetic chemists. Arguable the biggest impediment in devising such a method is to overcome the severe steric encumbrance faced in the bond-forming event. Therefore only a relatively limited range of both highly selective and mild methods are available.[474-483] Palladium catalyzed asymmetric allylic alkylation also known as the Tsuji-Trost reaction has become one of the most efficient ways to construct C-C bonds with high levels of enantioselectivity. The stoichiometric allylic allylation was discovered more than 40 years ago by the Tsuji group and subsequently developed into a catalytic version by Trost and co-workers. Later developments by Hayashi,[484] Ito,[485-488] Trost,[489-491] and Dai[492] and their co-workers have led to asymmetric allylic alkylation of prochiral stabilized enolates providing an important method for

synthesizing all-carbon quaternary stereocenters (Scheme 5.28). In the realm of asymmetric allylic alkylation these reactions are rather unusual since the newly formed stereocenter is situated on the nucleophilic coupling partner.[493,494]



Scheme 5.28 Asymmetric allylic alkylation with stabilized enolates.

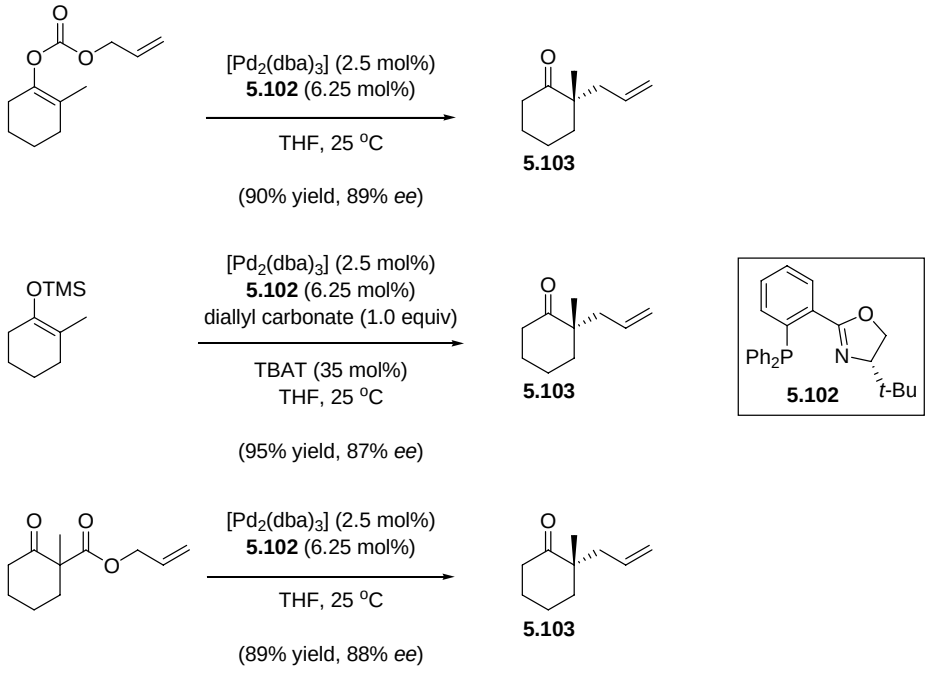
One important limitation that has hampered this methodology is the requirement that the carbon nucleophile is a soft carbanion, typically derived from stabilized enolates 25. With the disclosure of protocols from Trost and co-workers[495] and Dai and co-workers[496] the first steps to overcome this impediment were taken (Scheme 5.29). Utilizing the C_2-symmetric ligands **5.99** and **5.100** Trost[495] and Dai[496], respectively, were able to demonstrate that the asymmetric allylation of tetralone **5.101** was feasible through the lithium enolate (Scheme 5.29).



Scheme 5.29 Asymmetric allylic alkylation with unstabilized enolates.

One inherent limitation for these later protocols is that there must be only one acidic site or a large pK_a-difference between two acidic sites in the system to circumvent formation of mixtures of allylated products due to *in situ* enolate scrambling. Based on the pioneering work of Tsuji and co-workers[497-500] and Saegusa and co-workers,[501] this caveat was finally overcome by elegant contributions from Stoltz' and Trost' laboratories starting in the mid 2000s. In 2004 Behenna and Stoltz explored chelating P/N ligands to develop an enantioselective Tsuji-allylation from allyl enol carbonate substrates relying on *in situ* generation of the unstabilized enolate, thus avoiding the use

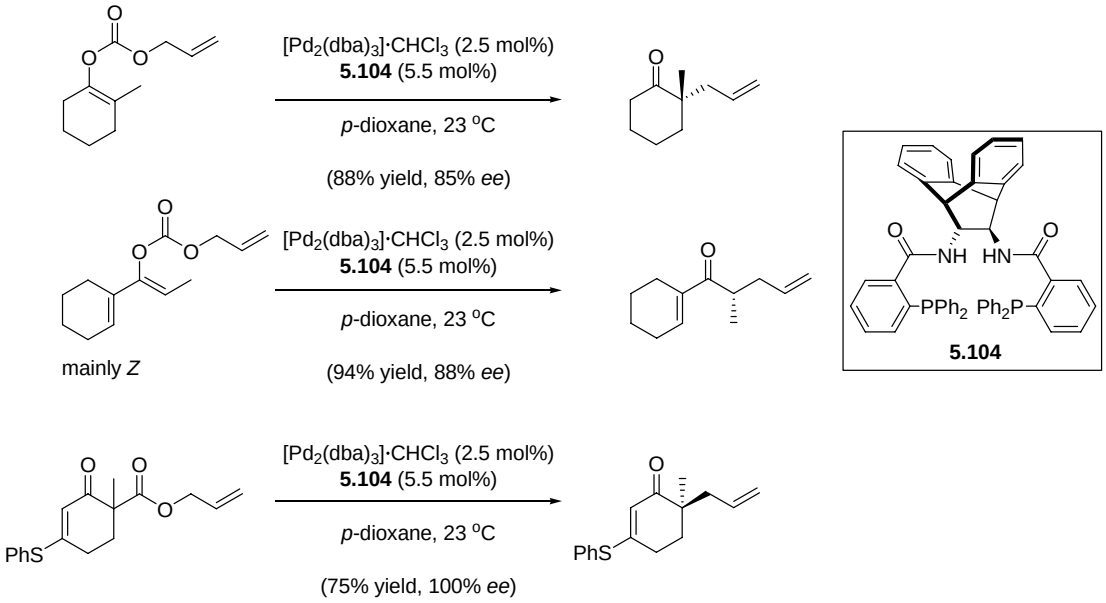
of stoichiometric amounts of base and enolate scrambling (Scheme 5.30).[415] Specifically, the *tert*-butyl phosphinooxazoline (*t*-BuPHOX, **5.102**) ligand framework developed in the 1990s by Pfaltz[502] and Williams[503] led to the formation of **5.103** in excellent yield and with high *ee*. Interestingly, a range of solvents including ethereal (THF, *p*-dioxane, Et_2O, *tert*-butyl methyl ether, *i*-Pr_2O), aromatic (benzene, toluene), and carbonyl-containing (EtOAc) proved to be almost equally effective. Later developments by Stoltz and co-workers extended the asymmetric method methodology to encompass silyl enol ethers[415,504] and β-ketoesters.[414] Notably, the ketones produced from allyl β-ketoesters, allyl enol carbonates, and silyl enol ethers were formed in nearly identical yield and *ee*. The asymmetric alkylation employing racemic β-ketoesters involves a stereoablative enantioselective transformation.[505] Initial deallylation of substrate of the β-ketoester followed by decarboxylation provides the prochiral enolate, which is enantioselectively alkylated.



Scheme 5.30 Enantioenriched cyclic ketones from allyl enol carbonates, silyl enol ethers and β-ketoesters.

In early 2005 Trost described a similar technology using the uniquely shaped bidentate phosphine ligand **5.104**. This method was applied to a number of cyclic ketones two of which contained more than one acidic site (Scheme 5.31).[506] Interestingly, *p*-dioxane proved to be the superior solvent for these reactions suppressing overalkylation for a range of substrates. Further studies by the Trost

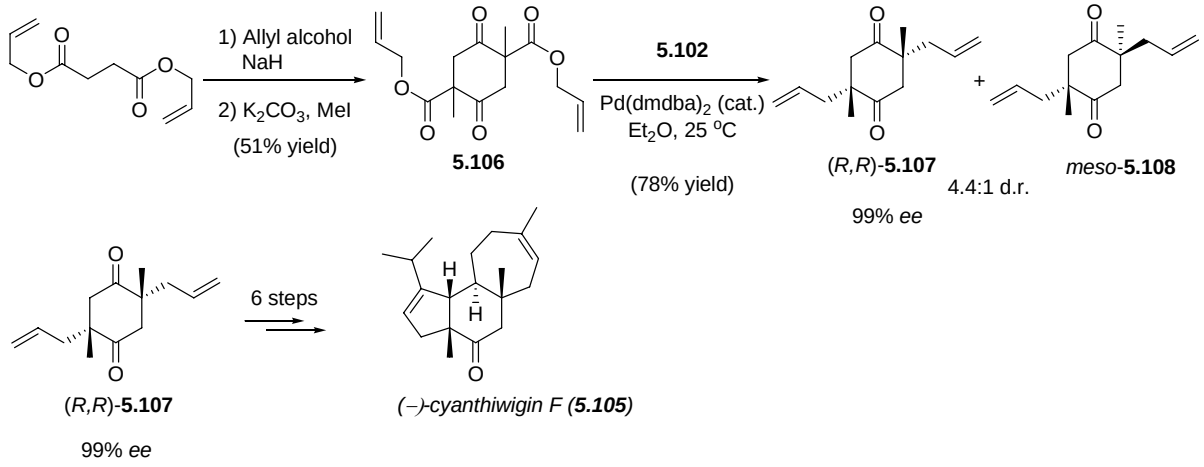
laboratory revealed that this catalyst system was also applicable to acyclic enol carbonates and vinylogous thioester enolates generated from the corresponding allyl *β*-ketoester.



Scheme 5.31 Implementation of **5.104** for asymmetric allylation of unstabilized enolates.

A notable feature of this chemistry is that the major enantiomer of the cycloalkanone product is the opposite when compared to previous work using similar ligands in the same enantiomeric series and preformed lithium enolates (cf. Scheme 5.29). This reversal in stereochemical outcome suggests that different mechanisms are operating.

Hitherto, the asymmetric Tsuji allylation have seen relatively sparse use in total synthesis, thus most of the examples originate from the Stoltz[507-512] and Trost[513-516] laboratories. However, the prevalence of all-carbon quaternary stereocenters in natural products provides an excellent testing ground for the enantioselective Tsuji allylation. One class of compounds that pose this structural feature is a group of diterpernoids known as the cyanthins which include the tricyclic ketone (−)-cyanthiwigin F (**5.105**; Scheme 5.32). Recently, a double catalytic enantioselective Tsuji allylation took center stage in the enantioselective synthesis of (−)-cyanthiwigin F (**5.105**) by Enquist and Stoltz.[510]

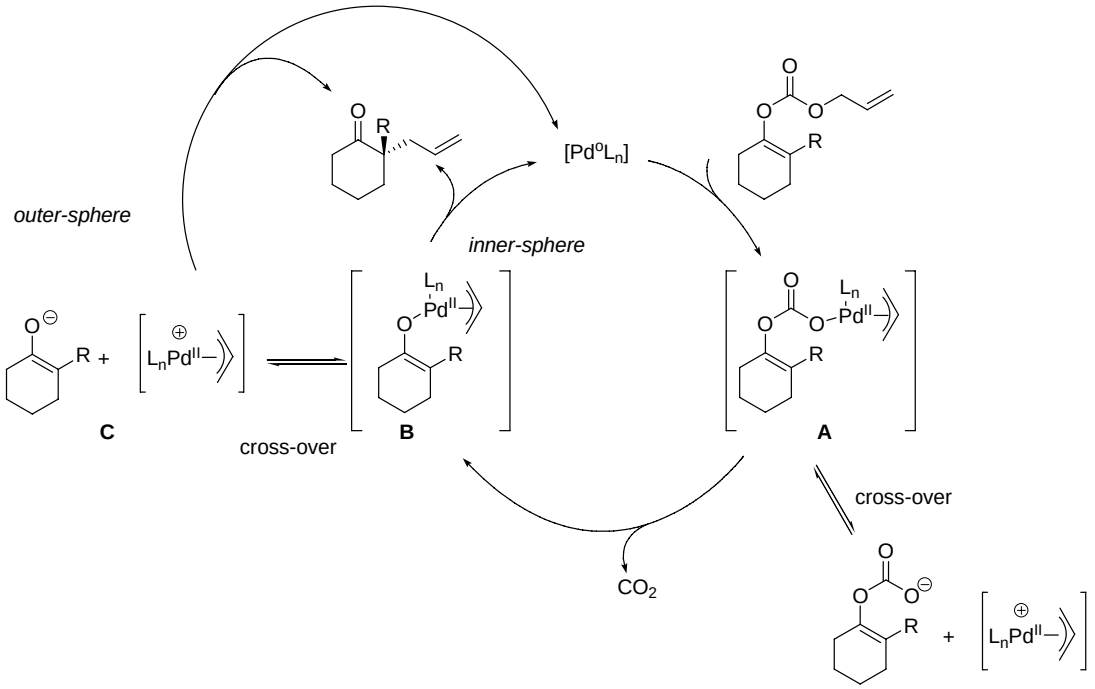


Scheme 5.32. Double catalytic enantioselective Tsuji-allylation in the total synthesis of (–)-cyanthiwigin F (**5.105**).

Treatment of a diastereomeric mixture (or either pure diastereomer) of bis(*β*-ketoester) **5.106** with $Pd(dmdba)_2$ (5 mol%) and **5.102** (5.5 mol%) provided the bisalkylated products (*R*,*R*)-**5.107** and *meso*-**5.108** in a 4.4:1 diastereomeric ratio. The *ee* of the major diastereomer was found to be 99% *ee*. Two all-carbon quaternary stereocenters were formed in this single catalytic step, thus addressing what is arguable the most challenging structural features of (–)-cyanthiwigin (**5.105**) in an elegant and highly efficient manner. Notably, the *ee* of the desired diastereomer (*R*,*R*) was 99% and this increase occurs by virtue of the heterochiral diastereomer *meso*-**5.108** acting as a "buffer" against formation of the undesired enantiomer *i.e.* the major diastereomer has experienced statistical amplification of its *ee* in line with the Horeau principle.[517,518] Conversion of bisketone **5.107** into **5.105** was achieved in six steps providing (–)-cyanthiwigin F in nine steps from diallyl succinate.

The mechanistic scenario of the Tsuji-allylation has hitherto not been subject to thorough investigations. In 1980 Saegusa and co-workers reported cross-over with a non-enantioselective system and allyl *β*-ketoesters in DMF, however cross-over was suppressed when the reaction was conducted in benzene.[501] To account for these results Saegusa proposed the catalytic cycle depicted in Scheme (5.33). The reaction is initiated by coordination of the allyl moiety to palladium followed by oxidative addition providing *π*-allylpalladium(II) compound **A**. This compound undergoes decarboxylation to afford a complex with the enolate coordinated to palladium **B** which upon reductive elimination could afford the allylated product via an inner-sphere process. Alternatively,

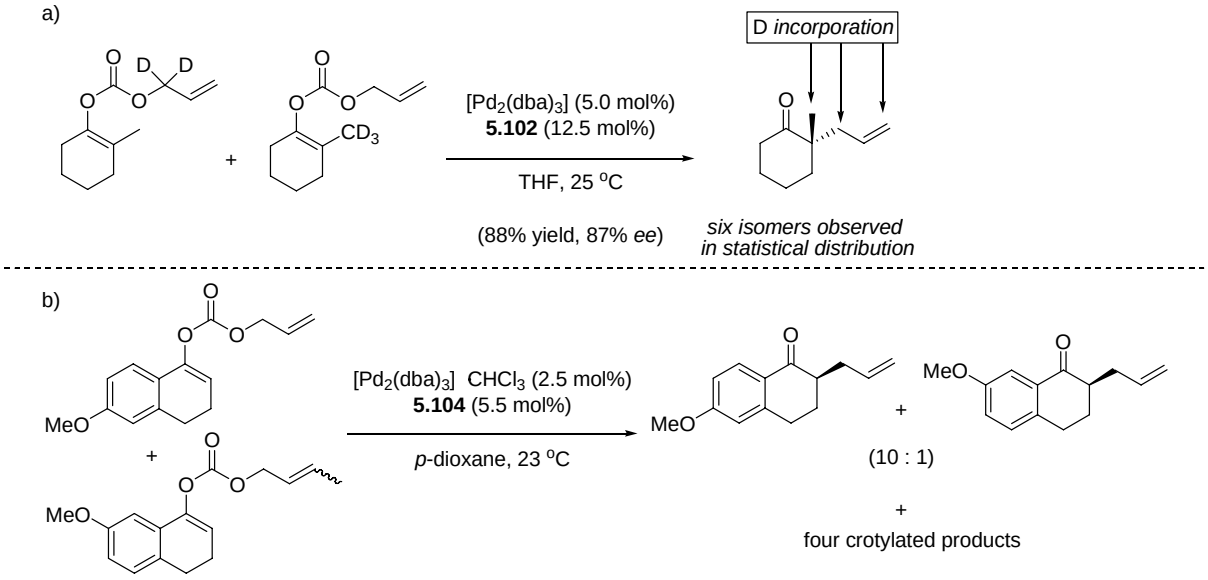
dissociation of the enolate forms a cationic π-allylpalladium(II) complex **C** which when attacked by the enolate anion generates the product by an outer-sphere process.



Scheme 5.33 Possible catalytic cycle for the decarboxylative allylation.

Later investigations by Stoltz and co-workers have shown scrambling of allyl termini and complete cross-over between differently deuteurated allyl enol carbonates in THF, *p*-dioxane and benzene suggesting the existence of a "discrete ketone enolate" (Scheme 5.34a). In contrast to these results Trost and co-workers observed only minor cross-over between allyl and crotyl carbonates (Scheme 5.34b). The latter observation may be explained by the existence of a solvent caged contact ion-pair. This rationale is further substantiated by the fact that utilizing *p*-dioxane solvent was important in order to suppress overalkylation and enolate scrambling.[a]

[a] *p*-Dioxane has been shown to form solvent-caged contact ion-pairs more efficiently than THF. (Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1965,** *87*, 669-670).

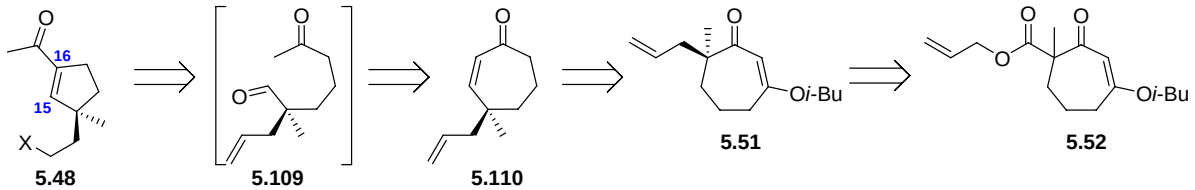


Scheme 5.34 Cross-over experiments conducted by a) Stoltz and b) Trost.

The cross-over experiments, however, are not instructive as to the mechanism of the C-C bond forming event or the origin of enantioselectivity. Recent computational modeling on the PHOX/Pd system supports the possible intermediacy of an inner-sphere palladium enolate **B** (cf. Scheme 5.33) rather than the outer-sphere nucleophile typical of traditional π-allyl alkylations.[519] This would be consistent with the high regiochemical fidelity observed throughout these studies and could be an explanation as to why high *ee's* can be obtained without prochiral allyl fragments.

5.5.2 Retrosynthesis of the D-Ring Fragment

In targeting the acylcyclopentene **5.48** we envisioned a scission of the C(15)-C(16) double bond employing an intramolecular aldol condensation of ketoaldehyde **5.109** (Scheme 5.35). Ketoaldehyde **5.109** could arise from cycloheptanone **5.110** which could result from vinylogous ester **5.51** utilizing a Stork-Danheiser-type transformation.[520] This vinylogous ester would ultimately be available by enantioselective decarboxylative alkylation of β-ketoester **5.52**.

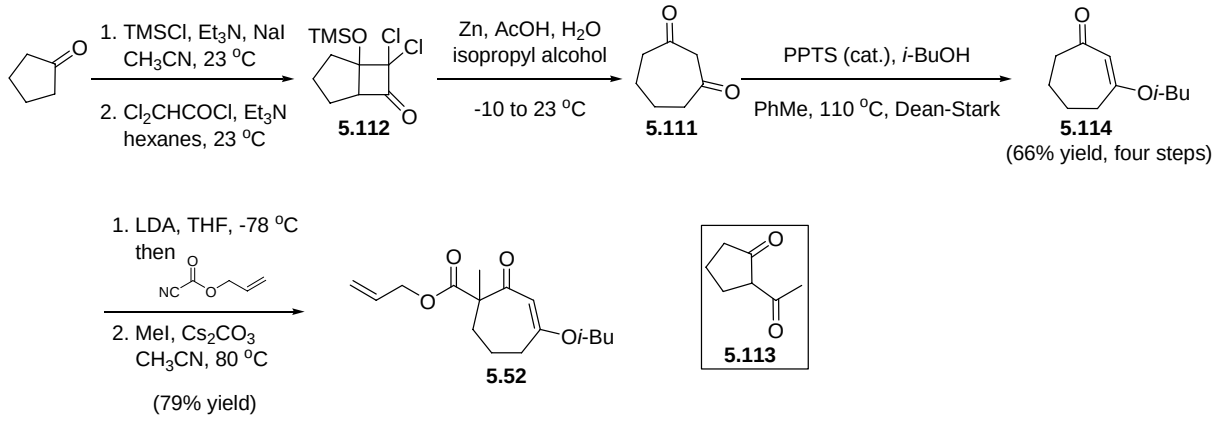


Scheme 5.35 Retrosynthesis of the D-ring fragment.

Even though the γ-disubstituted acylcyclopentane moiety has a high prevalence among terpene natural products, the synthesis of this type of building blocks has attracted very little attention. To the best our knowledge there is only one prior example detailing studies on the synthesis of racemic acylcyclopentenes.[521]

5.5.3 Asymmetric Synthesis of the D-Ring Fragment[a]

Implementation of the asymmetric decarboxylative Tsuji-allylation required efficient access to β-ketoester **5.52**. Although diketone **5.111** is commercially available, we decided to initiate the synthesis from cyclopentanone, since **5.111** decomposes upon storing and in addition its cost was prohibitive to our synthetic endeavors.[b] There have been several synthetic approaches to diketone **5.111**.[522-528] However, we settled for the synthetic sequence developed by Ragan and co-workers[529] since it avoids the use of heavy metal reagents and most importantly is amenable to large-scale preparation. Utilizing a sequence consisting of TMS-enolether preparation, [2+2] cycloaddition with *in situ* generated dichloroketene, and subsequent zinc-AcOH mediated reduction we were able to routinely prepare cycloheptadione **5.111** of suitable quality for further reactions on a 25 g scale in an overall yield of 79% starting from cyclopentanone (Scheme 5.36).



Scheme 5.36 Synthesis of β-ketoester **5.52**.

As previously noted by Ragan[530] we observed that the success of the zinc-AcOH reduction relied heavily on temperature control during the addition of AcOH to the mixture of cyclobutanone **5.112**, isopropyl alcohol and zinc. If the temperature rose above 0 °C we observed 5-20% formation of

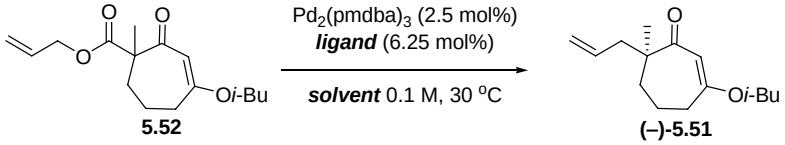
[a] The research described in chapter 5.5.3 was carried out in collaboration with Ph.D. student Michael R. Krout.
[b] 1,3-Cycloheptanedione is commercially available the approximate price per mole is $31,000. Adopted from Aldrich May 22th 2009.

acylcyclopentanone **5.113** which most likely occurs from C-C bond fragmentation (cleavage of silyl) prior to complete dechlorination. The formation of this byproduct could be almost completely suppressed when a mixture of MeOH and ice was deployed for efficient cooling. Reaction of 1,3-cycloheptanedione **5.111** with *iso*-butanol under Dean-Stark conditions in the presence of PPTS smoothly produced vinylogous ester **5.114**. Formation of *β*-ketoester **5.52** was achieved using acylation conditions inspired by work from Mander and co-workers.[531] Vinylogous ester **5.114** was treated with LDA and allyl cyanoformate furnishing the C-acylated product cleanly as judged by ^{1}H NMR of the crude reaction mixture. This material was exposed to MeI and Cs_2CO_3 in CH_3CN affording *β*-ketoester **5.52** in 79% yield over the two steps.

With *β*-ketoester **5.52** in hand the stage was set for installation of the quaternary stereocenter at C(14) implementing the asymmetric decarboxylative allylation. When *β*-ketoester **5.52** was treated with $Pd_2(pmdba)_3$ and (*S*)-*t*-BuPHOX **5.102** under standard allylation conditions[414] it was readily converted into allyl ketone ester **5.51** in good yield and 84% *ee* (Table 5.2, entry 1). The absolute stereochemistry depicted for **5.51** is based on analogy to previously reported substrates. This initial result serves as a promising lead for further optimization and emphasizes the utility of vinylogous ester substrates in the asymmetric Tsuji-allylation. Although recent studies have revealed that the electronics of dba-type ligands can have a significant influence on the reaction rate of palladium couplings,[532-535] the decision to implement $Pd_2(pmdba)_3$ as the source of palladium(0) was founded on practical considerations: dibenzylidene acetone (dba) was difficult to separate from the ketone product **5.51** while the more polar *para*-methoxy dibenzylidene acetone (pmdba) was easily removed.[a] In order to increase the *ee* we investigated a range of different solvents. Compared to previous results (cf. chapter 5.5.1) the employment of different solvents had a notable effect on the enantioselectivity. In the event we observed an inverse relationship between solvent dielectricity and enantioselectivity, *i.e.*, a significant increase in *ee* from 84% to 88% manifested itself when going from THF to PhMe (Table 5.2, entries 1 to 5).

[a] Control experiments have revealed that $Pd_2(dba)_3$, $Pd(dmdba)_2$, and $Pd_2(pmdba)_3$ provide yields and *ee*'s within experimental error.

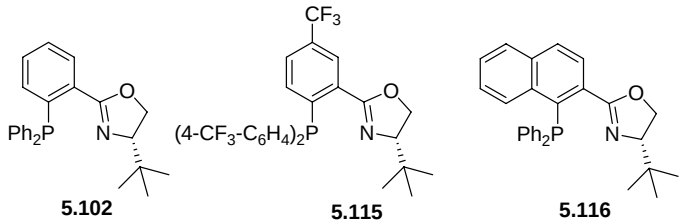
Table 5.2 Ligand screen for the enantioselective Tsuji-allylation.



5.52 **(–)-5.51**

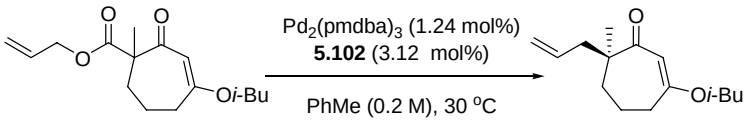
entry	ligand	solvent[a]	yield (%)[b]	ee (%)
1	**5.102**	THF	94	84
2	**5.102**	TBME	88	85
3	**5.102**	Et_2O	93	86
4	**5.102**	PhH	84	86
5	**5.102**	PhMe	91	88
6	**5.115**	PhMe	57[c]	90
7	**5.116**	PhMe	77	72

[a] Identical results obtained at 0.2 M in **5.52**. [b] Isolated yield. [c] 5 mol% of $Pd_2(pmdba)_3$ and 12.5 mol% **5.115** required to reach complete conversion.



5.102 **5.115** **5.116**

In an attempt to further increase *ee* we exposed *β*-ketoester **5.52** to the electron deficient phosphine **5.115**.[536] This did in fact furnish an increase in *ee* to 90%, however the yield dropped significantly and it was necessary to use 10 mol% palladium to obtain reasonable conversion of the substrate (Table 5.2, entry 6). Furthermore the active complex generated from ligand **5.115** and $Pd_2(pmdba)_3$ appeared to be highly sensitive to air. Employing the novel naphthyl-based phosphine **5.116** unfortunately lead to a decrease in yield and *ee*. Consequently, we settled for a catalyst system consisting of $Pd_2(pmdba)_3$ and (*S*)-*t*-BuPHOX **5.102** in PhMe which provided the best compromise between yield, *ee*, and practicality.

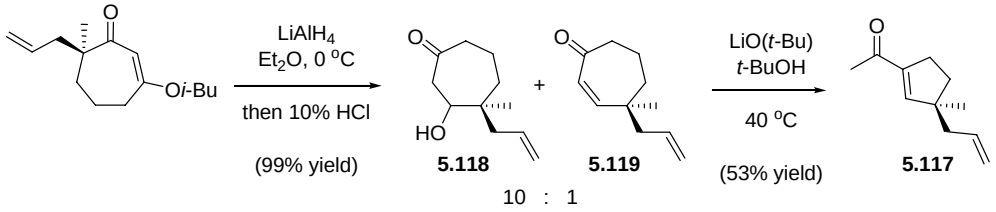


(–)-5.51
36 mmol scale

Scheme 5.37 Large scale asymmetric Tsuji-allylation.

For scale-up purposes we found that the catalyst loading could be reduced to 1.2 mol% and the substrate concentration increased to 0.2 M thus keeping the catalyst concentration constant. The best yield was obtained when the reaction was conducted on 36 mmol scale affording the desired ketone **5.51** in an excellent 98% yield and 88% *ee* (Scheme 5.37).

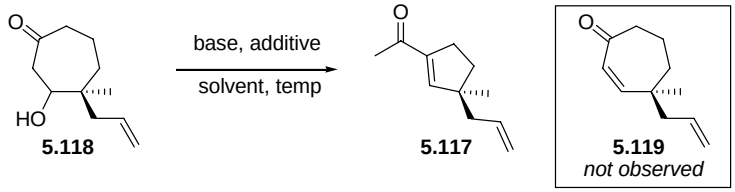
With a route to the enantioenriched *β*-ketoester **5.51** firmly established, ways to perform the ring contraction to **5.117** was explored. Treating *β*-ketoester **5.51** with lithium aluminium hydride followed by an acidic work-up smoothly provided a mixture of *β*-hydroxyketoester **5.118** and the desired cycloheptanone **5.119** in a 10:1 ratio (Scheme 5.38).



Scheme 5.38 Initial investigations on the ring contraction.

When a (10:1) mixture of *β*-hydroxyketoester **5.118** and cycloheptanone **5.119** was exposed to standard basic aldol conditions the requisite ring-contraction product **5.117** was obtained along with minor amounts of cycloheptanone **5.119**. This preliminary result suggested that cycloheptanone **5.119** was not readily being converted into acylcyclopentene **5.117**. Moreover, these compounds were very difficult to separate using silca-gel chromatography. Hence in order to improve the yield of this ring contraction, we decided to separate the mixture of *β*-hydroxyketoester **5.118** and cycloheptanone **5.119** and subject **5.118** to a range of different mild aldol conditions (Table 5.3). When the reaction was conducted in *t*-BuOH in the presence of a variety of *tert*-butoxide bases, LiO(*t*-Bu) presented itself as a good promoter for this retro-aldol aldol sequence (entries 1-4). Notably, switching to even milder reaction conditions using Cs_2CO_3 or LiOH as base and the non-nucleophilic alcohol CF_3CH_2OH[537] as additive the reaction cleanly provided the prerequisite product **5.117** (entries 5 to 11).

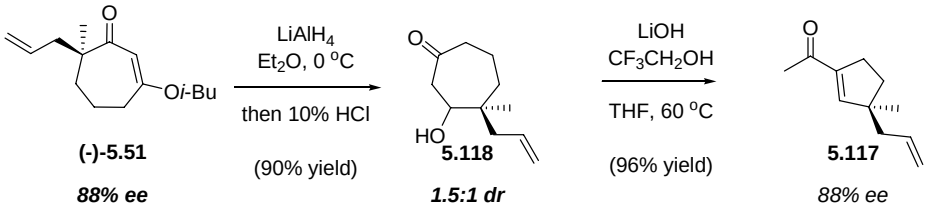
Table 5.3 Optimization of the ring-contraction.



entry	base	additive	solvent (0.1 M)	T(°C)	% yield[a]
1	LiO(*t*-Bu)	-	*t*-BuOH	40	68
2	NaO(*t*-Bu)	-	*t*-BuOH	40	52
3	KO(*t*-Bu)	-	*t*-BuOH	40	38
4	LiO(*t*-Bu)	-	THF	40	64
5	Cs_2CO_3	-	THF	60	15
6	Cs_2CO_3	*t*-BuOH	MeCN	40	32
7	Cs_2CO_3	*i*-PrOH	MeCN	40	34
8	Cs_2CO_3	CF_3CH_2OH	MeCN	40	71
9	Cs_2CO_3	CF_3CH_2OH	THF	60	79
10	LiOH	CF_3CH_2OH	MeCN	40	27
11	LiOH	CF_3CH_2OH	THF	60	80

[a] Yield judged by ^{1}H NMR.

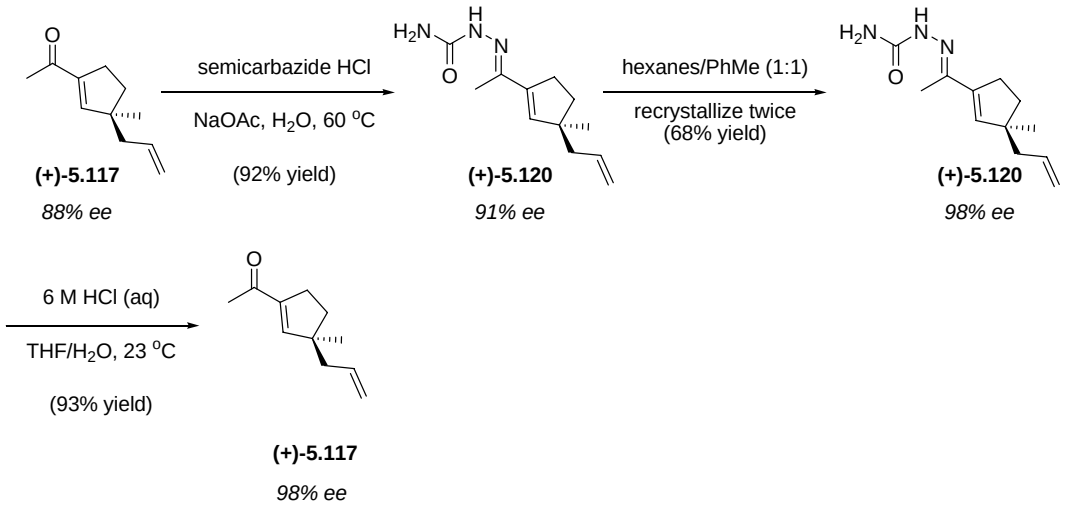
In scaling up this reaction we settled for the LiOH-mediated ring-contraction (Scheme 5.39). Using these optimized conditions *β*-hydroxyketoester **5.118** was isolated in 90% yield as a semicrystalline compound. Subsequent treatment with LiOH furnished acylcyclopentene **5.117** in 96% yield. Importantly, **5.117** was somewhat volatile so care had to be taken when concentrating this compound after silca-gel chromatography.



Scheme 5.39 Optimized synthesis of acylcyclopentene **5.117**.

Even though the asymmetric Tsuji-allylation provided enone **5.117** with high *ee* it was desirable to improve the *ee* of this material. Until this point all synthetic intermediates had been oils, hence it was decided to explore ways to attain crystalline material from **5.117**. Previous experience from the Stoltz laboratory[415,507] had shown semicarbazone derivatives to be suitable for this purpose. To our delight semicarbazone **5.120** was obtained as a white solid when enone **5.117** was treated with

semicarbazide hydrochloride in the presence of methanol, H_2O and pyridine at reflux providing **5.120** in (84-86)% yield, the *ee* had increased slightly to 91% (determined by converting **5.120** back into enone **5.117**) (Scheme 5.40). After some experimentation it was found that utilizing a biphasic system with NaOAc as the base consistently provided yields above 90% and the desired semicarbazone could easily be recovered by filtration when the reaction mixture had cooled to ambient temperature, again a slight increase in *ee* to 91% was observed.



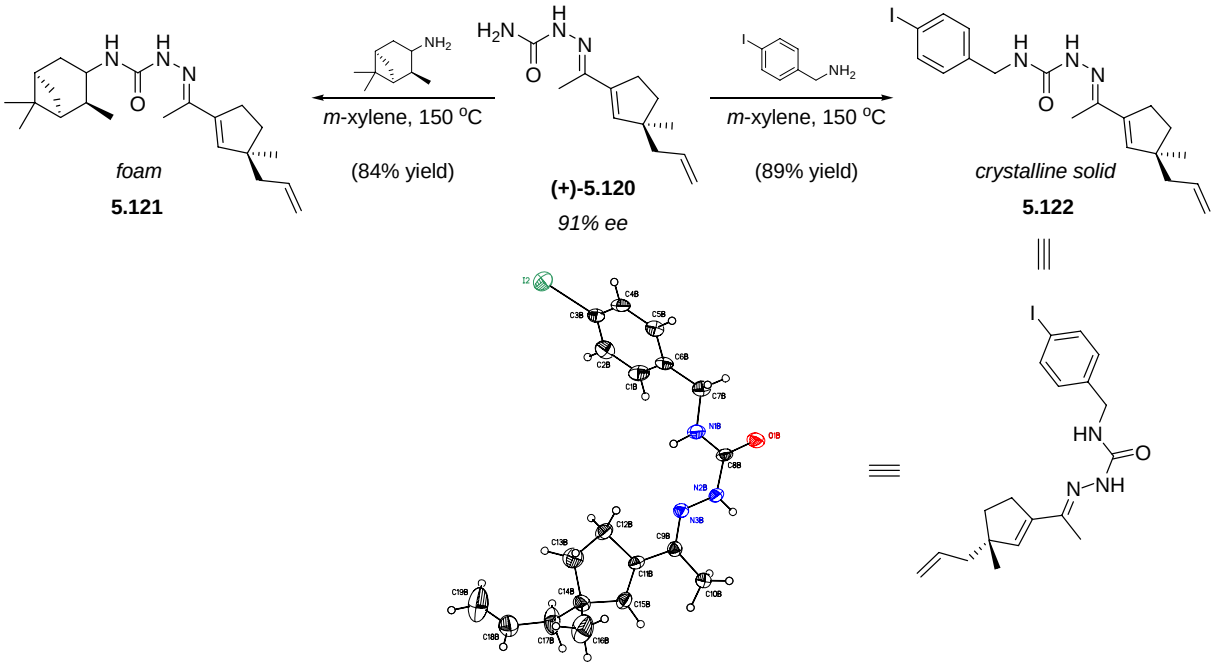
Scheme 5.40 Enantioenrichment of enone **5.117**.

In order to improve the *ee* further, suitable recrystallization conditions had to be established. It took significant experimentation to discover that the semicarbazone **5.120** could be recovered in 68% yield providing a satisfying 98% *ee* after two recrystallizations from a mixture of hexanes and PhMe (1:1). Notably, stirring during the crystallization proved to be essential for the efficiency of the *ee* improvement. Without stirring product recovery was comparable, however an unstirred crystallization provided semicarbazone **5.120** of 94% *ee*, while the stirred crystallization provided semicarbazone of 98% *ee* (both after two crystallizations). The enantioenriched semicarbazone was easily reverted back into enone **5.117** by treatment with aqueous HCl at ambient temperature.[a]

Thus far the absolute configuration of *β*-ketoester **5.51** and derivatives has been based on analogy. To verify this assignment it was decided to derivatize semicarbazone **5.120** and thereby attain the absolute configuration through X-ray crystallographic analysis. Initial attempts to derivatize

[a] These experiments served to illustrate that it was possible to increase the *ee* of **5.117** by derivatization/recrystallization. In general, however, the 88% *ee* material was carried on.

semicarbazone **5.120** with (+)-isopinocampheylamine were met with limited success since the resulting derivative **5.121** was attained as a foam which even after extensive screening of crystallization conditions would not afford crystals of X-ray quality (Scheme 5.41). Consequently, we focused our attention on the semicarbazone derivative **5.122** which was easily obtained by heating **5.120** dissolved in *m*-xylene in the presence of 4-iodobenzyl amine. It was found that slow vapor diffusion of pentane into a chloroform solution of **5.122** furnished crystals suitable for X-ray. Satisfyingly, the X-ray structural analysis confirmed the absolute configuration of the Tsuji-allylation.

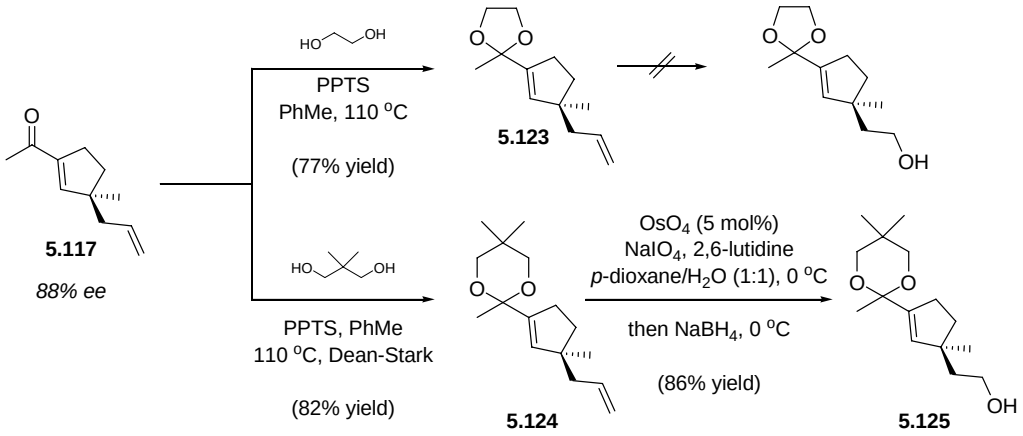


Scheme 5.41. Determination of the absolute configuration of the D-ring fragment.

With access to large quantities of enone **5.117**, more than 15 g was prepared underscoring the efficiency of the synthetic route, we began searching for an appropriate blocking group for the carbonyl moiety of this enone. The blocking group should withstand conditions allowing for oxidative cleavage, reduction, and subsequent iodination. Initially we tested the dioxolane **5.123** formed by treating acylcyclopentenone **5.117** with ethylene glycol and PPTS under Dean-Stark conditions (Scheme 5.42). [a] We were aware of the fact that this dioxolane might be easily

[a] These initial experiments with **5.123** were in fact carried out with racemic material, but to avoid confusion the correct stereochemistry is shown. This D-ring fragment has been synthesized using the route described to the enantioenriched fragment. The only difference was that the Tsuji-allylation was performed with an achiral version of the PHOX-ligand (cf. Chapter 5.8.4 for ligand syntheses).

hydrolyzed since it was situated in an allylic position. Therefore we decided to employ modified Johnson-Lemieux[538] conditions for the oxidative cleavage *i.e.* OsO_4-$NaIO_4$ in various solvents mixtures *e.g.* organic solvent- phosphate buffer (pH = 7.0) (1:1 to 3:1), comprising organic solvents such as THF, acetone, and *p*-dioxane. This resulted in a very slow reaction exhibiting low selectivity for the terminal alkene. Moreover, the dioxolane was readily hydrolyzed under these conditions as revealed by TLC.

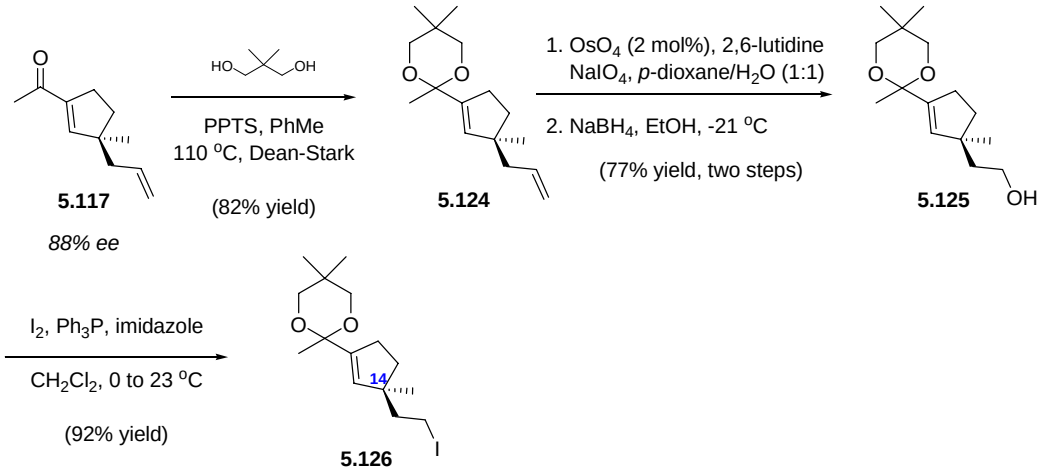


Scheme 5.42 Regioselective oxidative cleavage.

A recent report by Jin and co-workers[539] stated how the addition of pyridine and 2,6-lutidine significantly increased the reaction rate of the OsO_4-$NaIO_4$-mediated oxidative cleavage. Hence we decided to test pyridine and 2,6-lutidine with OsO_4-$NaIO_4$ in a 3:1 mixture of *p*-dioxane-H_2O. This did afford a fast conversion of **5.123** even at 0 °C (full conversion within 2 h), however we still observed hydrolysis of the dioxolane. Accordingly, it was determined to employ the acetal **5.124** generated from neopentyl glycol and **5.117**. Delightfully, dioxane **5.124** cleanly provided the oxidative cleavage when subjected to 2,6-lutidine with OsO_4-$NaIO_4$ in a 3:1 mixture of *p*-dioxane-H_2O at 0 °C as judged by ^{1}H NMR of the crude mixture. Furthermore when this reaction mixture was quenched with $NaBH_4$ the prerequisite alcohol **5.125** was attained in excellent yield. This one-pot protocol constitutes a highly efficient way to transform a terminal alkene into the corresponding one-carbon shortened primary alcohol.

Having identified an efficient route to the primary alcohol **5.125** we were eager to advance material toward the D-ring fragment. Acylcyclopentene **5.117** was protected implementing the optimized conditions which proceeded smoothly on gram scale, however it was found that the reductive work-

up of the oxidative cleavage was impractical on more than 1 gram scale since the exothermic nature of the quench necessitated slow addition of $NaBH_4$ (Scheme 5.43). In addition the presence of large amounts of dissolved borate salts eventually mediated hydrolysis of the acetal protecting group. Thus we decided to implement a two-step procedure involving a crude work up of the intermediate aldehyde followed by standard $NaBH_4$ reduction at -21 °C. The ensuing primary alcohol **5.125** was easily converted into the D-ring fragment **5.126** by treatment with PPh_3, imidazole and iodine.

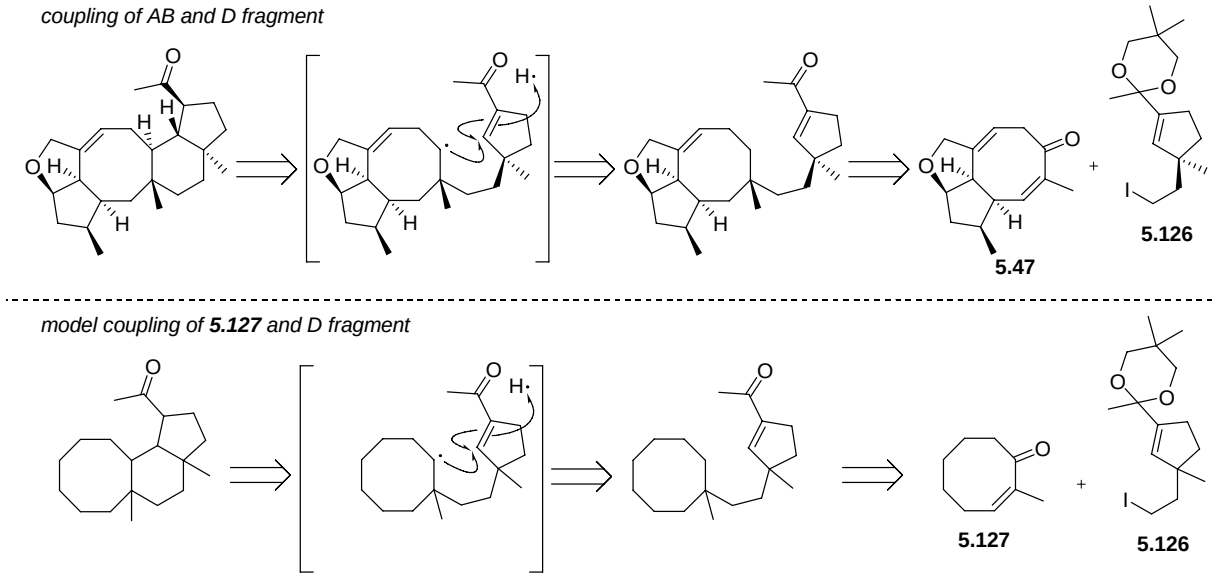


Scheme 5.43 Completion of the D-ring fragment.

In summary, an efficient route affording the D-ring fragment **5.126** in high *ee* has been developed starting from easily available 1,3-cycloheptadione. Key to this achievement was the successful implementation of the enantioselective decarboxylative allylation of a seven-membered vinylogous ester setting the all-carbon quaternary stereocenter at C(14) and the realization of the retro-aldol-aldol ring-contraction forming the five-membered D-ring.

5.6 Fragment Coupling and Radical Cyclization Studies

As previously detailed we envisioned that variecolin could be simplified into two major fragments by disconnection of the C-ring, coupled by a reductive alkylation/cyclization sequence in the forward sense (Scheme 5.44). In order to evaluate the potential of the coupling reaction for the union of our two major fragments **5.47** and **5.126** as well as the crucial conjugate intramolecular radical cyclization, model studies were undertaken. As our model we settled for the eight-membered enone **5.127**. While this enone **5.127** is far from as rigid as the AB-ring fragment **5.47** we anticipated that the conformational constraints imposed on **5.127** by transannular strain would display the obstacles concerned with the conjugate reduction/alkylation sequence.

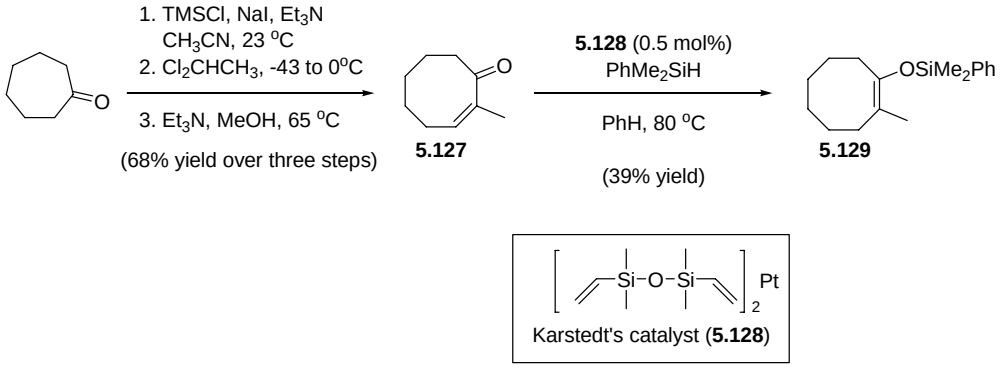


Scheme 5.44 Variecolin end-game model.

5.6.1 Model Studies on the Reductive Coupling

Our model enone **5.127** was readily available following the procedure of Conia and co-workers.[540] Cycloheptanone was converted into the corresponding silyl enol ether utilizing standard conditions. The ensuing enol ether was reacted with chlormethylcarbene generated *in situ* from 1,1-dichloroethane and *n*-BuLi to afford a diastereomeric mixture of chlorosiloxycyclopropanes (Scheme 5.45). Heating this material in methanol and triethyl amine provided the desired cyclooctenone **5.127** rearrangement and concomitant elimination of TMSCl.

Initially we sought to mediate the coupling of our model enone **5.127** and the D-ring fragment **5.126** by conjugate reduction and trapping the enolate *in situ*. We deployed a range of different conditions known to facilitate 1,4-reduction including: Stryker´s reagent $[(Ph_3P)CuH]_6$,[541,542] MeCu (cat.)/DIBAL,[543] L-selectride,[544] K-selectride,[545] and CuI/*n*-Bu_3SnH/LiCl[546] and attempted to trap the generated enolate with the highly potent electrophile MeI. However, we either observed no reaction or 1,2-reduction.

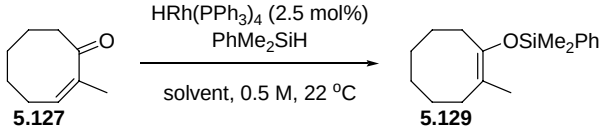


Scheme 5.45 Initial attempt to hydrosilylate enone **5.127**.

The fact that our attempts to achieve conjugate reduction utilizing metal hydrides provided mainly 1,2-reduction seemed to indicate that the conjugation between the carbonyl and the α,β-alkene is less pronounced than for the corresponding five- and six-membered ring systems that readily undergoes 1,4-reduction.[541-546] A plausible explanation is that the eight-membered ring, in order to allow for efficient overlap between the two π-orbital systems, would have to adopt a ring conformation disfavored by transannular strain.[547] Recognizing this impediment we shifted our focus to implementing a two step procedure involving transition metal catalyzed hydrosilylation and subsequent alkyl lithium mediated alkylation. Our initial investigations were aimed at applying the hydrosilylation procedure developed by Johnson and Raheja[548] to form triisopropsilyl enol ethers from cyclic enones using Karstedt's catalyst **5.128** and $(i\text{-Pr})_3SiH$. After surveying a range of different silanes $(i\text{-Pr})_3SiH$, Et_3SiH and $PhMe_2SiH$ we found that exposing enone **5.127** to 0.5 mol% **5.128** and $PhMe_2SiH$ provided the desired silyl enol ether **5.129** in a moderate yield. Unfortunately all attempts to improve this yield further were futile. Therefore a selection of Rhodium(I) complexes including, Wilkinson's catalyst $Rh(PPh_3)_3Cl$,[549] Browns catalyst ($[Rh(NBD)(DIPHOS\text{-}4)]BF_4$]),[550] and $HRh(PPh_3)_4$[551,552] known to facilitate similar reactions were tested in order to find a catalyst that would mediate this transformation. Of the catalysts tested $HRh(PPh_3)_4$ proved superior providing the

desired silyl enol ether cleanly after 48 h stirring at room temperature under neat reaction conditions as judged by ^{1}H NMR (Table 5.4). Despite the neat reaction conditions providing clean conversion of enone **5.127** into the desired silyl enol ether **5.129** these conditions were discarded for practical reasons.[a]

Table 5.4 Solvent screening for the hydrosilylation.

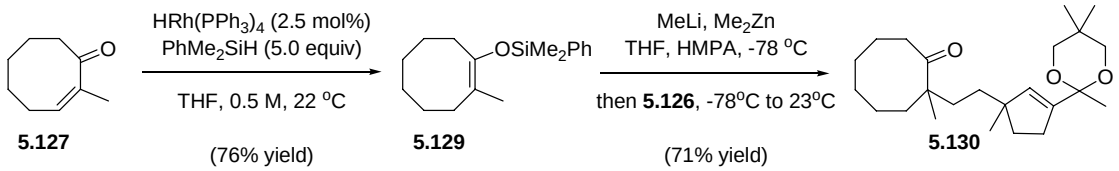


5.127 **5.129**

entry	$PhMe_2SiH$ (equiv)[a]	solvent	conversion (%)[b]	reaction time (h)
1	1.5	neat	90	48
2	1.5	PhH	70	48
3	1.5	PhMe	25	48
4	1.5	CH_2Cl_2	50	48
5	1.5	THF	90	48
6	1.5	THF	75	20
7	5.0	THF	>95	20
8	10.0	THF	>95	20

[a]Reactions were run on 0.18 mmol scale. [b]Conversion judged by ^{1}HNMR (clean conversion *i.e.* less than 5-10% byproducts).

Screening a range of different solvents (Table 5.4) revealed that THF afforded a faster reaction than less polar solvents such as benzene, toluene and dichloromethane (entries, 2 to 4). It was desirable to reduce reaction time by adding several equivalents of $PhMe_2SiH$ (entries 5 to 8). The use of five equivalents of $PhMe_2SiH$ allowed for clean conversion of enone **5.127** into **5.129** within 20 h stirring at 22 °C. Applying these optimized conditions afforded the silyl enol ether **5.129** in a satisfying 76% isolated yield (Scheme 5.46).



5.127 **5.129** **5.130**

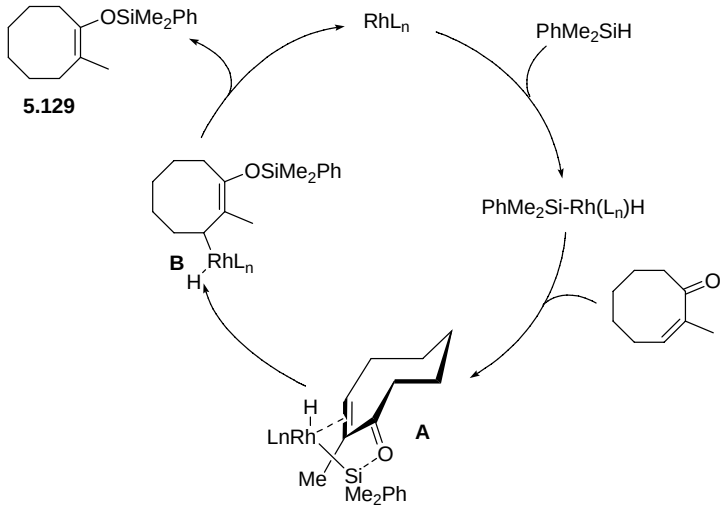
Scheme 5.46 Hydrosilylation and Noyori-type coupling.

The identification of suitable hydrosilylation conditions allowed us to investigate ways to mediate the alkylation of **5.129**. It was found that treating silyl enol ether with Noyori's modified alkylation conditions[553] provided the desired ketone **5.130** in a 71% yield as a 1:1.25 mixture of diastereomers

[a] It was expected that these reactions were to be conducted on a small scale rendering neat conditions impractical.

(Scheme 5.46).[a] Although the effect caused by adding dimethylzinc has not been investigated in detail ^{7}Li NMR experiments have suggested that there is a dynamic interaction between the lithium enolate and dimethylzinc possibly generating a lithium alkoxydialkyl zincate.[553] In any event conducting the alkylation in the absence of dimethyl zinc led to diminished yields due to lack of conversion.[b]

It is widely accepted that transition metal catalyzed hydrosilylation proceeds via initial coordination of a silyl metal hydride complex to the carbonyl oxygen (Scheme 5.47).[552,554] Zheng and Chan[552] have proposed simultaneous coordination to oxygen and alkene *i.e.* σ-coordination between oxygen and silicon and π-coordination between the metal and the double bond. This complex **A** rearranges with concomitant Si-Rh cleavage to afford intermediate **B** which upon reductive elimination furnishes silyl enol ether **5.129** and regenerates the catalyst.



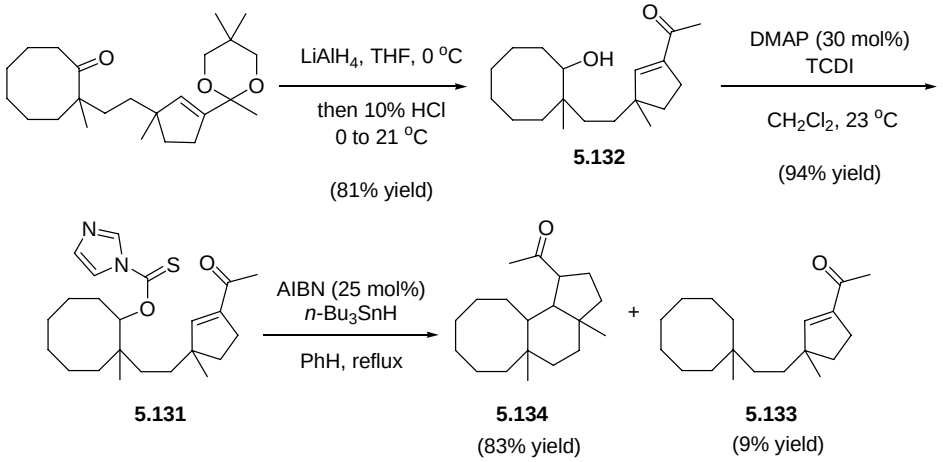
Scheme 5.47 Plausible mechanism for the hydrosilylation**.**

If this mechanism is operative it may provide a plausible reason to the successful implementation of the transition metal catalyzed hydrosilylation in the eight-membered enone **5.127** case. It seems fair to assume that the simultaneous coordination of carbonyl and alkene could override the effect of any conformational preferences leading to a low degree of conjugation in the eight-membered ring-system and thereby facilitate the desired 1,4-hydrosilylation.

[a] These model studies have been conducted with a racemic D-ring fragment.
[b] Initial experiments were performed with the corresponding TMS enol ether readily available from cyclooctanone (cf. chapter 5.8.4). These experiments revealed that both HMPA and dimethylzinc were crucial additives.

5.6.2 Model Studies on the Radical Cyclization

With our hands now on the alkylated product **5.130** we were eager to advance the material to imidazoyl thiocarbonate **5.131** in order to explore the pivotal radical cyclization (Scheme 5.48). The seemingly trivial task of reducing ketone **5.130** with $NaBH_4$ under standard conditions was hampered by long reaction times and low yields. This inability to efficiently reduce ketone **5.130** may most reasonably be assigned to the severe steric hindrance caused by the α all-carbon quaternary stereocenter. Gratifyingly, switching to $LiAlH_4$ followed by aqueous acid work-up afforded the desired reduction and cleavage of the dioxane protecting group in a single operation. The alcohol **5.132** was isolated as a mixture of four diastereomers and no attempts were made to separate these. To effect radical formation we sought to implement a Barton-McCombie-type deoxygenation.[555] Therefore the diastereomeric mixture of alcohols **5.132** was transformed into imidazoyl thiocarbonate **5.131** through the action of TCDI and a catalytic amount of DMAP.[a] During the initial investigations on the radical cyclization it was revealed that combination of AIBN and *n*-Bu_3SnH afforded a cleaner and faster reaction than AIBN in combination with TTMS. Moreover it was found that slow addition of AIBN and *n*-Bu_3SnH (over 5 h) to a refluxing solution of **5.131** in benzene was crucial to minimize formation of deoxygenation product **5.133**. In the event radical cyclization of **5.131** furnished the requisite tricyclic system **5.134** as a mixture of diastereomers constituting the BCD ring system of the variecolin sesterterpenes in excellent yield along with minor amounts of the deoxygenated product **5.133**.



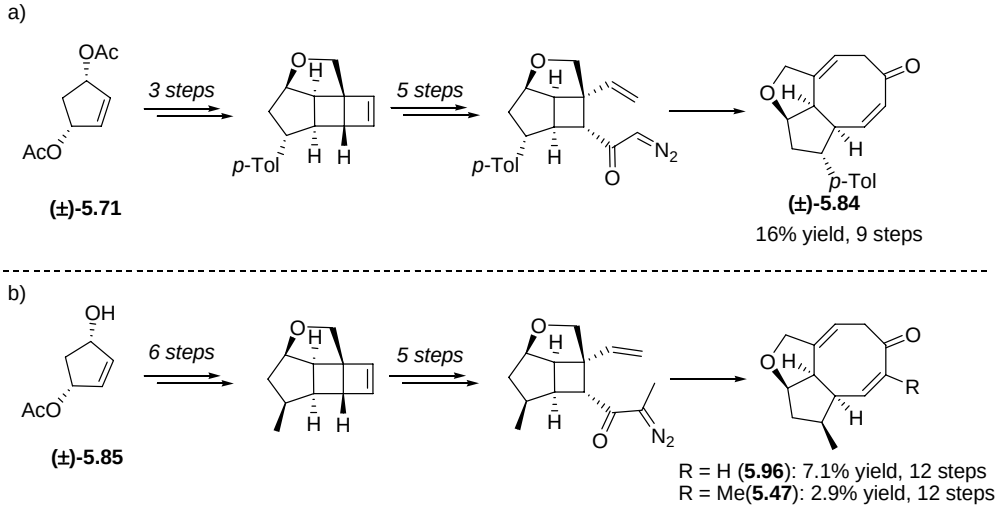
Scheme 5.48 End-game model studies.

[a] Attempts to install the thiocarbamate in the absence of DMAP resulted in sluggish reactions requiring reflux temperatures (1,2-dichloroethane or benzene as solvent) to reach full conversion. Moreover these conditions afforded up to 40% of an alkene product resulting from a Chugaev-type elimination.

In summary, these model studies have provided important information concerning the union of the AB-fragment and the D-fragment. A strategy to unite **5.126** and **5.127** through transition metal catalyzed hydrosilylation and alkylation has been developed. Moreover, conditions to facilitate the crucial conjugate radical cyclization have been discovered. While this model radical cyclization was unsuitable to afford information on the diastereoselectivity of this event it has provided important proof-of-principle for the tethered radical construction of the C(10)-C(15) bond in variecolin (**5.1**). Stereochemistry aside, these results have clearly shown that it should be feasible to couple the AB and D fragment and forge the C ring through a conjugate radical cylization thus affording a highly convergent approach to variecolin (**5.1**). Having reached this stage the authors external stay was coming to an end, however ongoing efforts by graduate student Michael R. Krout and Dr. Chris Henry[a] are directed toward assembling the AB-ring fragment and the D-ring fragment (cf. chapter 5.7).

5.7 Summary and Outlook

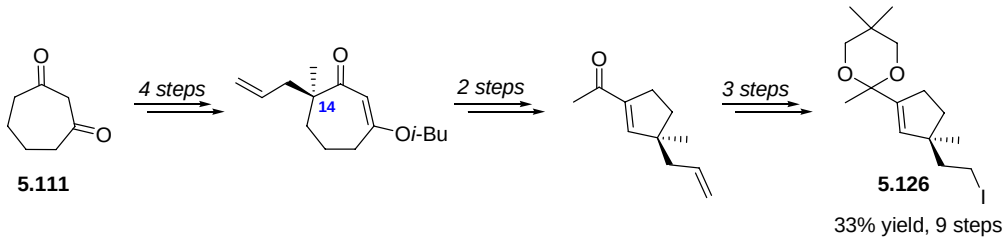
Until this point the project has culminated in efficient synthetic routes to the two major building blocks for variecolin. We have developed synthetic routes to the enantiopure AB-fragments **5.96** and **5.47** implementing the tandem Wolff-Cope to forge the central eight-membered ring. Hence we have successfully telescoped this methodology to the synthesis of highly functionalized eight-membered rings (Scheme 5.49).



Scheme 5.49 Synthesis of the AB-ring fragments.

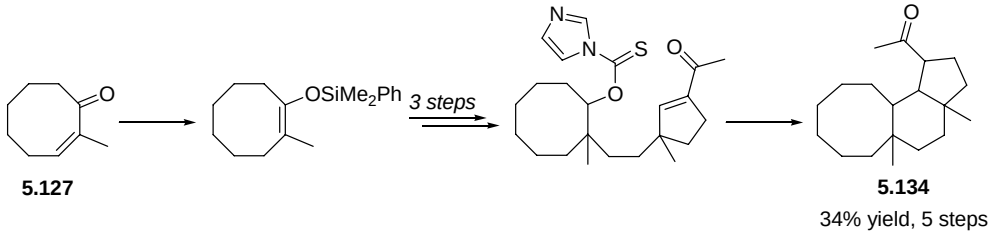
[a] Dr. Chris Henry joined the project a few months after the author's departure from Caltech.

Additionally, we have devised an efficient route to the D-ring fragment **5.126** in high *ee* starting from easily available 1,3-cycloheptadione. Key to this achievement was the successful deployment of the enantioselective decarboxylative allylation toward a seven-membered vinylogous ester constructing the all-carbon quaternary stereocenter at C(14) and realization of the retro-aldol-aldol ring contraction forming the five-membered D-ring (Scheme 5.50).



Scheme 5.50 Synthesis of the D-Ring fragment.

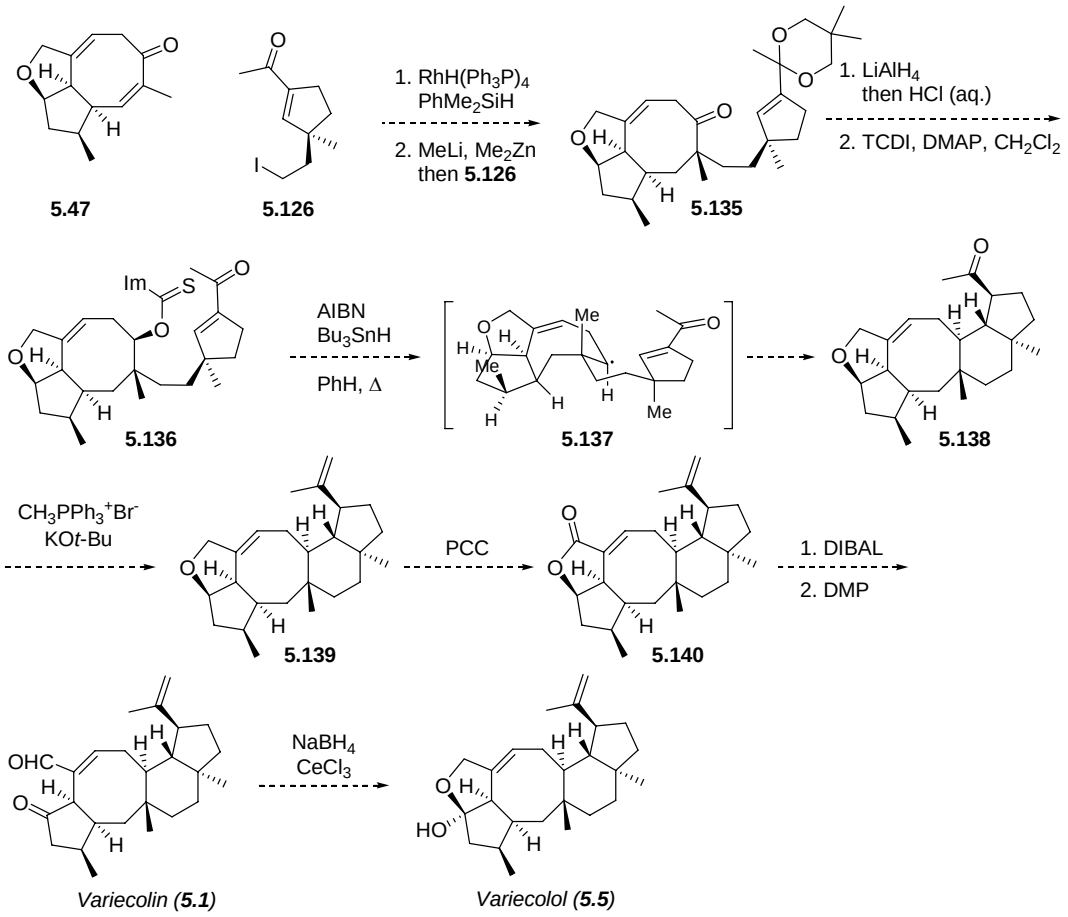
Finally, we have conducted model studies for the late stage coupling of the AB-ring fragment and the D-ring. These studies revealed the feasibility of performing a 1,4-hydrosilylation alkylation sequence followed by a conjugate radical cyclization to convergently combine the fragments and build the remaining C-ring (5.51).



Scheme 5.51 End-game model studies.

With asymmetric routes to the AB-fragment and the D-ring fragment established efforts are directed toward their efficient union through the two-step hydrosilylation Noyori-type alkylation pathway. We anticipate that the union of the AB-fragment **5.47** and D-fragment **5.126** will provide the depicted diastereomer (*i.e.* **5.135**) based on the concave nature of the tricyclic system (Scheme 5.52). The final C-C bond of the variecolin system will be formed using the radical cyclization conditions developed for the model system *i.e.* we expect that treating imidazoyl thiocarbonate **5.136** with Bu_3SnH and AIBN in refluxing benzene will generate the pentacyclic system **5.138**. The stereochemical outcome of the radical cyclization can be rationalized based on minimization of developing steric interactions in the transition state *i.e.* **5.137**. Most importantly, in the depicted

transition state model there are no severe 1,3-diaxial interactions developing while there is efficient orbital overlap between the sp^3-centered radical and the alkene of the cyclopentene moiety. We expect that the final stereocenter at C(16) will be set under thermodynamic control either during the radical cyclization or in course of the work-up. The completion of the entire variecolin skeleton will lead us directly into the end-game. Wittig methylenation of **5.138** followed by oxidation with PCC will furnish lactone **5.140**. Ultimately, DIBAL reduction of this and DMP oxidation will complete the total synthesis of variecolin (**5.1**).



Scheme 5.52 Proposed completion of variecolin (**5.1**) and congener variecolol (**5.5**).

Selective Luche reduction of the enal moiety will afford variecolol (**5.5**). Upon completion the synthesis of variecolin (**5.1**) will have been accomplished in a longest linear sequence of 21 steps. Moreover the synthetic route has showcased the adaptability of the Wolff-Cope rearrangement toward construction of highly functionalized cyclooctanoid systems. Additionally, the asymmetric

decarboxylative allylation have been implemented in an efficient synthesis of the potentially widely applicable acylcyclopentene building block.

5.8 Experimental Section

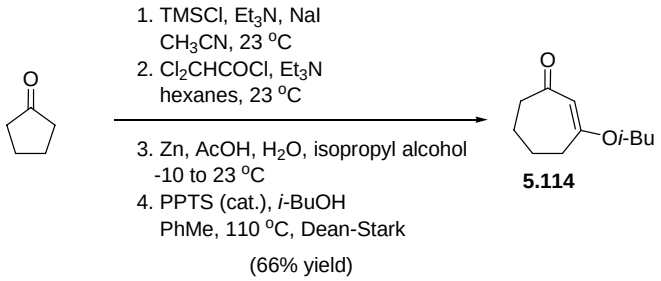
5.8.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF was distilled over sodium/fluoroenone and *p*-dioxane was distilled over sodium prior to use. Other solvents were dried by passage through an activated alumina column under argon. Diisopropylamine and triethylamine were distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Phosphinooxazoline ligands were prepared by methods described in our previous work.[415,536] Tris(4,4'-methoxydibenzylidene-acetone)dipalladium(0) was prepared according to the method of Ibers.[556] Allyl cyanoformate was prepared according to the method of Rattigan.[557] (*Z*)-2-Methyl-cyclooct-2-enone (**5.127**) was prepared according to the method of Conia.[540] Starting materials were purchased from Aldrich or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulater. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde or $KMnO_4$ staining. ICN silica gel (particle size 0.032-0.0653 mm) was used for flash chromatography. Silica gel impregnated $AgNO_3$ was prepared as follows: $AgNO_3$ (5.0 g) was dissolved in MeCN (15 mL), SiO_2 (15 g) was added the slurry was thoroughly mixed and dried under vacuum (2 h) to provide a free-flowing powder. ^1H NMR spectra were recorded on a Varian Mercury 300 MHz or a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6H_6 (δ 7.16 ppm). ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz or a Varian Inova 500 MHz spectrometer (at 75 MHz and 125 MHz respectively) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or C_6D_6 (δ 106 ppm). ^{31}P NMR were recorded on a Varian Mercury 300 MHz spectrometer at 121 MHz, and are reported relative to the external standard H_3PO_4 (0.0 ppm). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m

= multiplet, comp. m = complex multiplet, br s = broad singlet, app = apparent. Data for ^{13}C and ^{31}P NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter operating on the sodium D-line (254 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, *ee*). Melting points were measured using a Thomas-Hoover capillary melting point apparatus and the reported values are uncorrected. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility.

5.8.2 Synthesis of the Variecolin D-Ring Fragment

3-Isobutoxy-cyclohept-2-enone (5.114)



NaI (156.74 g, 1.05 mol) was placed in a 3-L 3-neck round bottom flask and dried under high vacuum at 90 °C for 12 h and then allowed to cool to 23 °C under N_2. CH_3CN (1.3 L) was added to dissolve the NaI. To the solution was added cyclopentenone (70.7 g, 74.3 mL, 0.84 mol) followed by Et_3N (106.25 g, 146.3 mL, 1.05 mol). The flask was fitted with an addition funnel, the funnel was charged with TMSCl (104.03 g, 122 mL), which was added dropwise over 30 min. The resulting suspension was stirred for an additional 1 h at 23 °C. Pentane (1.0 L) was added, and the biphasic system was stirred vigorously for 10 min. The layers were separated and the CH_3CN layer was extracted with pentane (3 x 400 mL). The combined pentane phases were washed with H_2O (2 x 500 mL), brine (500 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product (131.4 g, quantitative) as a colorless oil.

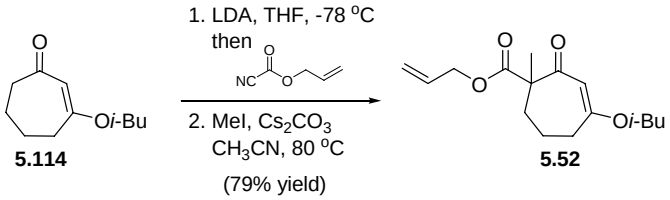
The above trimethylsilylether (89.7 g, 0.57 mol) was placed in a flame-dried 3-L 3-neck round bottom flask fitted with a stopper, an addition funnel, and an overhead stirrer. Hexanes (900 mL) were added followed by Et_3N (80.7 g, 111.2 mL, 0.798 mol). Dichloroacetyl chloride (101.70 g, 66.4 mL, 0.69 mol) was dissolved in hexanes (400 mL) and added dropwise over 9.5 h. After 18 h stirring at 23 °C, the brown suspension was filtered, rinsing with EtOAc (3 x 500 mL). The clear brown solution was concentrated under reduced pressure and then filtered through a pad of Al_2O_3 (7 x 18 cm, neutral) using EtOAc as eluent. The solution was concentrated under reduced pressure to afford the desired product (124.7 g, 82% yield) as a brown oil that crystallized in the freezer (-20 °C).

The above dichlorocyclobutanone (53.4 g, 0.2 mol) was placed in a 3-L 3-neck round bottom flask fitted with a thermometer, an addition funnel and an overhead stirrer. Isopropyl alcohol and purified water (170 mL each) were added, and the suspension was cooled to -10 °C (internally) by use of a MeOH/ice bath. Zn (58.8 g, 0.9 mol) was added in four portions (5 min between each) and AcOH (66.1 g, 63 mL, 1.1 mol) dissolved in H_2O (130 mL) was added in a dropwise manner, keeping the internal temperature below 0 °C (usually added over 1.5 h). The mixture was stirred for an additional 30 min at -10 °C (internally) then the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 8.5 h, the reaction mixture was filtered, elution with isopropyl alcohol (100 mL). The mixture was cooled to 0 °C and neutralized by portionwise addition of K_2CO_3 (74.6 g, 0.54 mol). The viscous suspension was filtered, elution with H_2O (100 mL) and EtOAc (300 mL). The biphasic system was concentrated under reduced pressure to ~200 mL and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired product (24.2 g, 96% yield) as a pale orange oil.

To a flask fitted with a Dean-Stark trap, a reflux condenser, and containing a solution of 1,3-cycloheptanedione[529] (35.8 g, 0.28 mol) in toluene (280 mL) was added *i*-butanol (168.3 g, 208 mL, 2.27 mol) and PPTS (1.07 g, 4.26 mmol). The solution was immersed into an oil bath at 130 °C and monitored by TLC. When the starting material was consumed (typically within 4-6 h), the reaction was allowed to cool to room temperature. The resulting dark orange solution was washed with saturated aqueous $NaHCO_3$ (200 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL), the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated under

reduced pressure to afford a thick dark orange oil. The crude oil was flushed through a plug of silica gel (7 x 9 cm SiO_2, 1:4→3:7→1:1 Et_2O-Hexanes) to afford the desired product **5.114** (43.5 g, 84% yield, 66% yield over 4 steps) as a pale orange oil; R_f = 0.22 (2:1 Hexanes-EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.49 (d, *J* = 6.6 Hz, 2H), 2.60-2.56 (comp. m, 4H), 2.00 (septuplet, *J* = 6.6 Hz, 1H), 1.88-1.77 (comp. m, 4H), 0.96 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\cdot}$: 182.1307; found 182.1310.

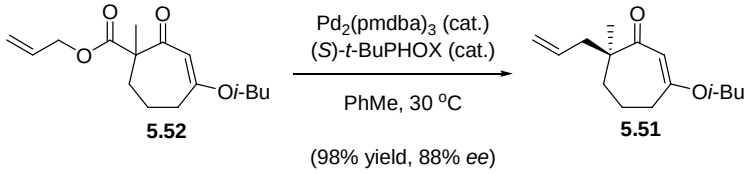
4-Isobutoxy-1-methyl-2-oxo-cyclohept-3-enecarboxylic acid allyl ester (5.52)



Diisopropyl amine (4.66 g, 6.46 mL, 46.1 mmol) was placed in a 500-mL round bottom flask, dissolved in THF (180 mL) and cooled to 0 °C by use of an ice/water bath. *n*-BuLi (17.2 mL, 44.2 mmol, 2.57 M in hexanes) was added dropwise over 15 min by use of syringe pump. After 15 min stirring at 0 °C, the mixture was cooled to -78 °C by use of an acetone/CO_2(s) bath. Vinylogous ester **5.114** (7.01 g, 38.4 mmol) was dissolved in THF (20 mL) and added in a dropwise manner over 20 min by use of a syringe pump. After an additional 1 h stirring at -78 °C, allyl cyanoformate (4.69 g, 4.60 mL, 42.2 mmol) was added in a dropwise manner over 10 min. The mixture was stirred at -78 °C for 2.5 h, quenched with saturated aqueous NH_4Cl and H_2O (30 mL each) and then allowed to warm to ambient temperature. The reaction mixture was diluted with Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a pale orange oil 10.5 g (>100%, some allyl cyanoformate left). The crude oil was placed in a 500 mL round bottom flask and dissolved in CH_3CN (130 mL). MeI (16.35 g, 7.2 mL, 115 mmol) was added to the reaction mixture followed by Cs_2CO_3 (16.76 g, 49.9 mmol), the flask was fitted with a condenser, immersed into an oil bath, and heated to 80 °C while stirring vigorously. After 12 h stirring at 80 °C, the reaction mixture was allowed to cool to ambient temperature, diluted with EtOAc (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to

afford an orange oil. The crude product was purified by flash chromatography (5 x 15 cm SiO_2, 19:1 → 9:1, Hexanes-EtOAc, dry-loaded using celite) to afford **5.51** (8.51 g, 79% yield) as a pale yellow oil; R_f = 0.43 (4:1 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, *J* = 17.1, 2.9, 1.5 Hz, 1H), 5.20 (app. d, *J* = 10.5 Hz, 1H), 4.64 (ddt, *J* = 13.3, 5.6, 1.2 Hz, 1H), 4.56 (ddt, *J* = 13.4, 5.6, 1.2), 3.50 (dd, *J* = 9.3, 6.8 Hz, 2H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.59 (ddd, *J* = 17.8, 9.8, 3.9 Hz, 1H), 2.45-2.38 (comp. m, 2H), 2.02-1.94 (m, 1H), 1.84-1.75 (m, 1H), 1.70 (ddd, *J* = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{16}H_{24}O_4$ $[M]^{+\cdot}$: 280.1675; found 280.1686.

(*S*)-7-Allyl-3-isobutoxy-7-methyl-cyclohept-2-enone (5.51)

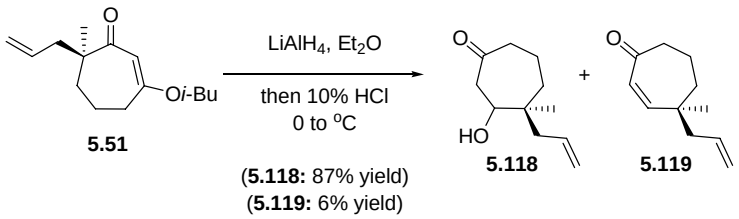


5.52 → **5.51** (98% yield, 88% *ee*)

$Pd_2(pmdba)_3$ (496 mg, 0.45 mmol) and (*S*)-*t*-BuPHOX **5.102** (439 mg, 1.13 mmol) were placed in a 500-mL round bottom flask. The flask was evacuated and backfilled with N_2 (3 cycles with 10 min evacuation per cycle). Toluene (150 mL, sparged with N_2 for 1 h immediately before use) was added and the black suspension was immersed into an oil bath preheated to 30 °C. After 30 min stirring, the *β*-keto-ester **5.52** (10.16 g, 36.2 mmol) was added as a solution in toluene (31 mL sparged with N_2 immediately before use) by use of positive pressure cannulation. The dark orange catalyst-solution turned olive green immediately after the addition of *β*-keto-ester **5.52**. The reaction mixture was stirred at 30 °C for 21 h, allowed to cool to ambient temperature, filtered through a plug of silica (5.5 x 2 cm SiO_2, Et_2O) and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 5 x 15 cm, 19:1 Hexanes-EtOAc, dry-loaded using SiO_2) to afford **5.51** (8.38 g, 98% yield) as a pale yellow oil; R_f = 0.31 (3:1 Hexanes-Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05-5.00 (m, 2H), 3.50 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.47 (dd, *J* = 9.3, 6.6 Hz, 1H), 2.53-2.42 (m, 2H), 2.38 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.20 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.98 (app septuplet, *J* = 6.6 Hz, 1H), 1.86-1.70 (comp. m, 3H), 1.62-1.56 (m, 1H), 1.14 (s, 3H), 0.95 (app d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7,

171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873, 1614, 1470, 1387, 1192, 1171, 998, 912 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{15}H_{24}O_2$ $[M]^{+\cdot}$: 236.1776; found 236.1767; $[\alpha]_D^{25.6}$ –69.04 ° (*c* 1.08, $CHCl_3$, 88.0% *ee*). HPLC conditions: 1% IPA, OD-H column, t_R (min): major = 6.30, minor = 7.26.

(*S*)-4-Allyl-3-hydroxy-4-methyl-cycloheptanone (5.118) and (*S*)-4-Allyl-4-methyl-cyclohept-2-enone (5.119)



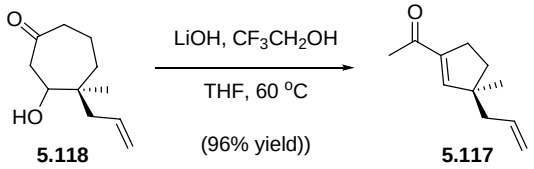
A 500-mL round bottom flask was charged with Et_2O (150 mL) and cooled to 0 °C by use of an ice/water bath. $LiAlH_4$ (806 mg, 21.2 mmol) was added in one portion. After 10 min was **5.51** (9.13 g, 38.6 mmol) added in a dropwise manner as a solution in Et_2O (43 mL) by use of positive pressure cannulation. The grey suspension was stirred for 40 min and $LiAlH_4$ (148 mg, 3.9 mmol) was added in one portion. After an additional 30 min stirring at 0 °C, the reaction was quenched by slow addition of HCl (110 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was azeotroped with toluene (3 x 20 mL) and purified using flash chromatography (SiO_2, 5 x 15 cm, 9:1→3:1 Hexanes-EtOAc, dry-loaded using celite) to afford **5.118** (6.09 g, 87% yield) and **5.119** (387 mg, 6.1% yield) both as colorless oils.

(5.118); R_f = 0.23 (7:3 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ **major epimer**; 5.88 (dddd, *J* = 15.1, 9.0, 7.6, 7.6 Hz, 1H), 5.12-5.08 (m, 2H), 3.70 (dd, *J* = 4.9, 3.9 Hz, 1H), 2.86 (dd, *J* = 15.6, 1.7 Hz, 1H), 2.65 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.54-2.43 (m, 2H), 2.24 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.07 (dd, *J* = 13.4, 7.3 Hz, 1H), 1.99 (dd, *J* = 15.9, 4.4 Hz, 1H), 1.82-1.69 (comp. m, 2H), 1.45-1.41 (m, 1H), 0.96 (s, 3H); **minor epimer** 5.83 (dddd, *J* = 14.9, 10.3, 7.6, 7.6 Hz, 1H), 5.12-5.06 (m, 2H), 3.68 (dd, *J* = 4.1, 2.4 Hz, 1H) 2.80 (dd, *J* = 15.4, 2.4 Hz, 1H), 2.74 (dd, *J* = 15.4, 8.1 Hz 1H), 2.46-

2.38 (m, 2H), 2.18 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.09 (dd, *J* = 12.9, 7.8 Hz, 1H), 1.82-1.65 (comp. m, 3H) 1.50-1.47 (m, 1H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ **major epimer**; 213.2, 135.0, 118.1, 72.9, 46.7, 44.9, 44.2, 41.0, 36.3, 21.9, 18.9; **minor epimer**; 212.6, 134.2, 118.3, 73.3, 47.2, 42.8, 41.0, 35.9, 22.6, 18.7; IR (Neat Film NaCl) 3436, 3074, 2932, 1692, 1638, 1443, 1403, 1380, 1352, 1318, 1246, 1168, 1106, 1069, 999, 913, 840 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{18}O_2$ $[M]^{+\cdot}$: 182.1313; found 182.1307.

(5.119); R_f = 0.54 (7:3 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 12.9, 0.7 Hz, 1H), 5.82 (d, *J* = 12.9 Hz, 1H), 5.75 (dddd, *J* = 17.1, 10.3, 7.8, 7.1 Hz, 1H), 5.10 (dddd, *J* = 10.3, 1.2, 1.2, 1.2 Hz, 1H), 5.08-5.03 (m, 1H), 2.65-2.52 (m, 2H), 2.19 (app dd, *J* = 13.7, 6.8 Hz, 1H), 2.11 (app dd, *J* = 13.7, 8.1 Hz, 1H), 1.84-1.76 (m, 3H), 1.68-1.63 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 152.5, 133.8, 128.6. 118.6, 47.2, 45.1, 42.7, 38.2, 27.1, 18.4; IR (Neat Film NaCl) 3076, 3011, 2962, 2934, 2870, 1659, 1454, 1402, 1373, 1349, 1335, 1278, 1208, 1172, 997, 916, 874, 822, 772 cm^{-1}; HRMS (EI) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^{+\cdot}$: 164.1201; found 164.1209; $[\alpha]_D^{21.0}$ –9.55 ° (*c* 1.07, $CHCl_3$, 88.0% *ee*).

1-((*S*)-3-Allyl-3-methyl-cyclopent-1-enyl)-ethanone (5.117)

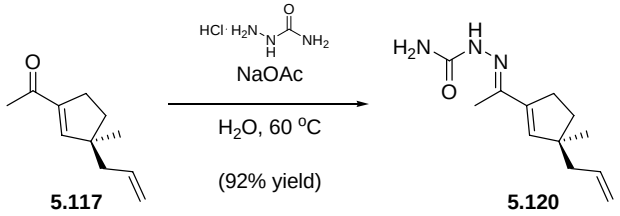


5.118 **5.117**

β-Hydroxyketoester **5.118** (6.09 g, 33.4 mmol) was placed in a 500-mL round bottom flask and dissolved in THF (334 mL). 2,2,2-Trifluoroethanol (5.04 g, 3.67 mL, 50.1 mmol) and LiOH (1.20 g, 50.1 mmol) were added, and the flask was fitted with a condenser, purged with N_2, and heated to 60 °C by use of an oil bath. After 18 h stirring, the suspension was allowed to cool to ambient temperature, diluted with Et_2O (150 mL), dried over Na_2SO_4 (30 min stirring), filtered, and concentrated carefully under vacuum allowing for a film of ice to form on the outside of the flask. The crude product was purified using flash chromatography (SiO_2, 5 x 15 cm, 15:1 Hexanes-Et_2O) to afford **5.117** (5.29 g, 96% yield) as a colorless fragrant oil; R_f = 0.67 (8:2 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (app t, *J* = 1.7 Hz, 1H), 5.76 (dddd, *J* = 16.4, 10.7, 7.3, 7.3 Hz, 1H), 5.07-5.03 (comp. m, 2H), 2.59-2.48 (m, 2H), 2.21-2.14 (m, 2H), 2.30 (s, 3H), 1.85 (ddd, *J* =

12.9, 8.3, 6.3 Hz, 1H), 1.64 (ddd, *J* = 6.1, 8.5, 12.9 Hz), 1.11 (s, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 151.9, 143.8, 134.9, 117.8, 50.0, 45.3, 36.0, 29.7, 26.8, 25.6; IR (Neat Film NaCl) 3077, 2956, 2863, 1668, 1635, 1616, 1454, 1435, 1372, 1366, 1309, 1265, 1213, 1177, 993, 914, 862 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{17}O$ [M+H] 165.1279; found 165.1281; $[\alpha]_D^{21.4}$ +17.30 ° (*c* 0.955, $CHCl_3$, 88.0% *ee*).

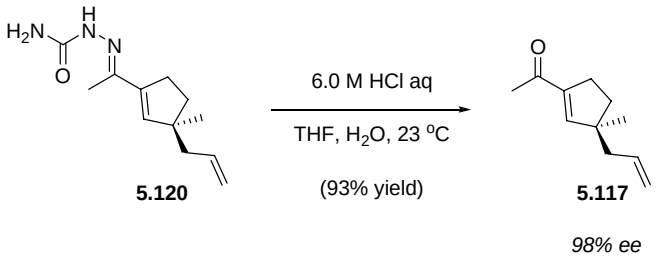
(1*E*)-1-(1-((*S*)-3-Allyl-3-methylcyclopent-1-enyl)ethylidene)semicarbazide (5.120)



A 15-mL round bottom flask was charged with sodium acetate (150 mg, 1.83 mmol), semicarbazide hydrochloride (204 mg, 1.83 mmol), and a magnetic stirbar. Purified water (1.7 mL) was added and the mixture was stirred until all the solids had dissolved. Acylcyclopentene **5.117** (250 mg, 1.52 mmol) was added neat and the mixture was heated to 60 °C for 4 h. The slurry was allowed to cool to ambient temperature while stirring and vacuum filtered (water aspirator). The white solid was dried under reduced pressure to afford **5.120** (311 mg, 92% yield). The *ee* of the semicarbazone at this point was found to be 91% (measured by hydrolysis to **5.117**). The semicarbazone **5.120** (300 mg, 1.36 mmol) was transferred to a round bottom flask, the solids were suspended in toluene-hexanes (50:50), and the mixture was heated to 90 °C while stirring. After a few minutes stirring, the solids had dissolved completely to afford a clear colorless solution. Heating was discontinued and the stirring mixture was allowed to cool to 23 °C while still immersed in the oil bath. After 10 h had elapsed, the slurry was vacuum filtered to afford **5.120** (246 mg, 82% yield). The *ee* at this point was found to be 94.5 % (measured by hydrolysis to **5.117**). A second recrystallization following the above procedure employing **5.120** (241 mg, 1.09 mmol) afforded **5.120** (201 mg, 83% yield). The *ee* at this point was found to be 97.9% (measured by hydrolysis to **5.117**); R_f = 0.30 (9:1 $CHCl_3$-MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 6.06 (br s, 1H), 5.85 (app t, *J* = 1.6 Hz, 1H), 5.76 (dddd, *J* = 16.7, 9.3, 7.4, 7.4 Hz, 1H), 5.47 (br s, 1H), 5.06-4.98 (comp. m, 2H), 2.67-2.49 (m, 2H), 2.15-2.12 (m, 2H), 1.98 (s, 3H), 1.82 (ddd, *J* = 12.8, 8.2, 6.9 Hz, 1H), 1.62 (ddd, *J* = 12.8, 8.5, 6.4 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 145.0, 141.7, 141.2, 135.6, 117.2,

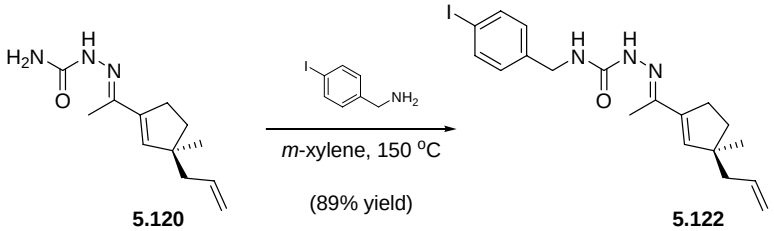
49.2, 45.9, 36.2, 30.8, 26.3, 12.8; IR (Neat Film NaCl) 3473, 3266, 3189, 2946, 2858, 1698, 1579, 1478, 1437, 1377, 1349, 1321, 1130, 1109, 993, 910, 845, 768 cm^{-1}; HRMS (TOF MS ES+) *m/z* calc'd for $C_{12}H_{20}N_3O$ $[M+H]^+$: 222.1606; found; 222.1610; $[\alpha]_D^{22.6}$ +39.80 ° (*c* 0.84, $CHCl_3$, 97.9% *ee*); mp =145-146 °C (1:1 toluene-hexanes).

1-((*S*)-3-Allyl-3-methyl-cyclopent-1-enyl)-ethanone (5.117)



Semicarbazone **5.120** (191.8 mg, 0.867 mmol) was dissolved in THF (1.92 mL) and HCl (3.84 mL, 6.0 M, in H_2O) was added. The resulting biphasic mixture was stirred vigorously at 23 °C for 30 h. The reaction mixture was diluted with Et_2O (10 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated carefully under vacuum allowing for a film of ice to form on the outside of the flask. The residue was filtered through a short pad of silica (1 x 10 cm SiO_2, 4:1 Hexanes:Et_2O) to afford **5.117** 132.6 mg (0.81 mmol, 93% yield); $[\alpha]_D^{22.6}$ +39.80° (*c* 0.84, $CHCl_3$, 97.9% *ee*).

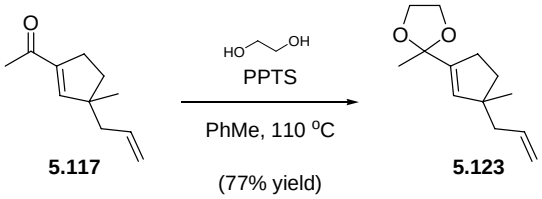
(1*E*)-4-(4-Iodobenzyl)-1-(1-((*S*)-3-allyl-3-methylcyclopent-1-enyl)ethylidene)semicarbazide (5.122)



To a solution of semicarbazone **5.120** (50 mg, 0.23 mmol, 91% *ee*) in *m*-xylene (2.2 mL) was added 4-iodo-benzylamine (63 mg, 0.27 mmol). The resulting pale yellow solution was immersed in an oil bath and heated to 150 °C. After 9 h stirring at 150 °C, the mixture was allowed to cool to ambient temperature and concentrated under reduced pressure to afford a pale yellow solid. The crude solid was purified by flash chromatography (1.0 x 15 cm SiO_2, 9:1 → 7:3 Hexanes:EtOAc) to afford

5.122 (88 mg, 89% yield) as a white solid. X-ray quality crystals were obtained by slow vapor diffusion of pentane into a chloroform solution of **5.122**; R_f = 0.52 (9:1 $CHCl_3$-MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.66-7.64 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.50 (t, *J* = 6.1 Hz, 1H), 5.86 (app t, *J* = 1.5 Hz, 1H), (dddd, *J* = 16.9, 9.0, 7.6,7.6 Hz, 1H), 5.04-5.01 (comp. m, 2H), 4.46 (d, *J* = 6.3 Hz, 2H), 2.60-2.49 (m, 2H), 2.18-2.10 (m, 2H); 1.95 (s, 3H), 1.82 (ddd, *J* = 12.9, 8.5, 6.3 Hz, 1H), 1.62 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 144.5, 141.5, 141.4, 139.2, 137.8, 135.6, 129.4, 117.2, 92.6, 49.3, 45.9, 43.2, 36.2, 30.9, 26.3, 12.5; IR (Neat Film NaCl) 3411, 3194, 3075, 2946, 2920, 2863, 1677, 1528, 1486, 1401, 1323, 1259, 1142, 1114, 1057, 1000, 913, 845 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}N_3OI$ $[M+H]^+$: 438.1043; found 438.1036; $[\alpha]_D^{22.2}$ +31.43 ° (*c* 0.36, $CHCl_3$, 91.0% *ee*); mp = 123-124 °C ($CHCl_3$-*n*-pentane).

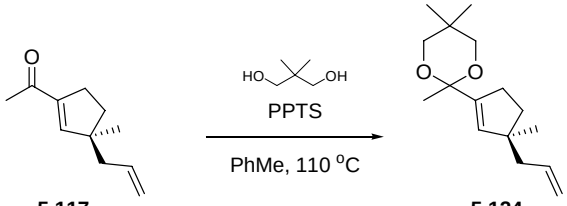
2-(3-Allyl-3-methyl-cyclopent-1-enyl)-2-methyl-[1,3]dioxolane (5.123)



Acylcyclopentene **5.117** (388.1 mg, 2.36 mmol) was placed in a 25-mL round bottom flask and dissolved in benzene (11.8 mL). Ethylene glycol (880 mg, 791 μL, 14.2 mmol) was added followed by PPTS (59.4 mg, 0.24 mmol), and the flask was fitted with a condenser and a Dean-Stark trap. The flask was immersed into an oil bath and heated to reflux (oil bath at 115 °C). After 18 h stirring at reflux, the mixture was allowed to cool to ambient temperature, diluted with Et_2O (50 mL), and washed with brine (10 mL). The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash chromatography (2 x 20 cm SiO_2, 15:1→ 9:1 Hexanes:EtOAc) to afford **5.123** (381.4 mg, 77% yield); R_f = 0.49 (7:3 Hexanes-EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (dddd, *J* = 17.1, 9.3, 7.6, 7.6 Hz, 1H), 5.50, (br s, 1H), 5.02-4.99 (comp. m, 4H), 3.98-3.84 (comp. m, 2H), 2.36 (dddd, *J* = 10.3, 8.1, 5.9, 1.7 Hz, 1H), 2.30 (dddd, *J* = 10.3, 8.1, 6.1, 1.7 Hz, 1H), 2.09 (d, *J* = 7.3 Hz, 2H), 1.82 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.62 (ddd, *J* = 12.7, 8.8, 5.9 Hz, 1H), 1.48-1.47 (m, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9,

136.0, 135.7, 116.8, 107.4, 64.7, 64.7 (two peaks), 48.4, 46.1, 36.8, 30.6, 26.5, 24.0; IR (Neat Film NaCl) 2951, 2888, 1454, 1372, 1192, 1108, 1043, 996, 946, 912, 858 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{17}O_2$ $[M - Me]^+$: 193.1229; found 193.1232.

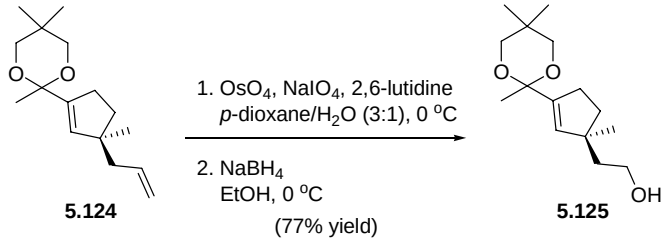
2-((*S*)-3-Allyl-3-methyl-cyclopent-1-enyl)-2,5,5-trimethyl-[1,3]dioxane (5.124)



5.117 **5.124**

Acylcyclopentene **5.117** (5.29 g, 32.2 mmol) was placed in a 1-L round bottom flask and dissolved in toluene (322 mL). Neopentyl glycol (20.1 g, 193.2 mmol) was added followed by PPTS (809 mg, 3.22 mmol) and the flask was fitted with a Dean-Stark trap and a condenser. The mixture was placed in an oil bath and heated to reflux (oil bath at 135 °C). After 25 h stirring, the mixture was allowed to cool to ambient temperature, diluted with Et_2O (250 mL), and poured into saturated aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with Et_2O (2 x 100 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white semi-solid. The crude product was purified by flash chromatography (7.0 x 25 cm SiO_2, hexanes $\rightarrow$ 99:1 $\rightarrow$ 98:2 Hexanes:EtOAc) to afford **5.124** (6.59 g, 82% yield) as a pale yellow oil; R_f = 0.62 (7:3 Hexanes-EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dddd, *J* = 16.7, 9.3, 7.4, 7.4 Hz, 1H), 5.52 (app t, *J* = 1.8 Hz, 1H), 5.06-4.99 (comp. m, 2H), 3.59 (dd, *J* = 11.2, 0.8 Hz, 1H), 3.51 (dd, *J* = 11.2, 0.8 Hz, 1H), 3.31 (d, *J* = 11.2 Hz, 2H), 2.37-2.19 (m, 2H), 2.13 (app dt, *J* = 7.4, 1.1 Hz, 2H), 1.853 (ddd, *J* = 12.8, 8.2, 6.4 Hz, 1H), 1.63 (ddd, *J* = 12.8, 8.8, 6.1 Hz, 1H), 1.41 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 138.2, 136.1, 116.9, 98.8, 71.8, 71.7, 49.0, 46.2, 36.4, 31.4, 29.8, 27.8, 26.9, 22.8, 22.2; IR (Neat Film NaCl) 3075, 2952, 2906, 2868, 1640, 1472, 1455, 1182, 1118, 1041, 996, 950, 911, 862 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{27}O_2$ $[M+H]^+$: 251.2011; found 251.2011; $[\alpha]_D^{20.9}$ +11.48 ° (*c* 1.01, $CHCl_3$, 88.0% *ee*).

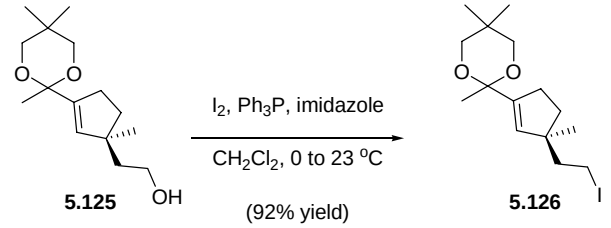
2-[(*S*)-1-Methyl-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-2-enyl]-ethanol (5.125)



5.124 **5.125**

Dioxane **5.124** (1.51 g, 6.0 mmol) was dissolved in 1,4-dioxane (45 mL) and purified H_2O (15 mL) was added followed by 2,6-lutidine (1.29 g, 1.40 mL, 12.0 mmol). The mixture was cooled to 0 °C by use of an ice/water bath and then $NaIO_4$ (5.13 g, 24.0 mmol) was added followed by OsO_4 (30.5 mg, 0.12 mmol). The resulting suspension was stirred for 4.5 h at 0 °C and then filtered, rinsing with EtOAc (100 mL). The aqueous phase was separated and extracted with EtOAc (2 x 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product 1.82 g (>100 %, contains some 2,6-lutidine) as a clear brown oil. The crude product was dissolved in EtOH (7.5 mL) and cooled to -21 °C by use of a MeOH/ice bath. $NaBH_4$ (227.0 mg, 6.0 mmol) was dissolved in EtOH (7.5 mL), precooled to 0 °C, and added dropwise over 25 min to the reaction mixture by use of positive pressure cannulation. After an additional 1 h stirring at -21 °C, the reaction was quenched by slow addition of H_2O (4.5 mL). The reaction mixture was allowed to warm to 0 °C, concentrated under reduced pressure to ~10 mL and extracted with CH_2Cl_2 (3 x 25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a pale brown oil. The crude product was purified by flash chromatography (3.0 x 15 cm SiO_2, 19:1 → 9:1 → 4:1 Hexanes:EtOAc) to afford **5.125** 1.18 g (4.6 mmol, 77% yield) as a pale yellow oil. R_f = 0.38 (7:3 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (app t, *J* = 1.7 Hz, 1H), 3.71 (ddd, *J* = 7.3, 7.3, 5.4 Hz, 2H), 3.52 (app t, *J* = 11.0 Hz, 2H), 3.34 (11.0 Hz, 2H), 2.38-2.26 (m, 2H), 1.88 (ddd, *J* = 12.9, 8.5, 6.1 Hz, 1H), 1.71 (t, *J* = 7.3 Hz, 2H), 1.69 (ddd, *J* = 12.9, 8.5, 5.9 Hz, 1H), 1.42 (s, 3H), 1.21 (t, *J* = 5.1 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H). 0.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 138.1, 98.6, 71.7, 60.2, 47.3, 44.1, 36.9, 31.1, 29.5, 29.5, 27.4, 27.1, 22.7, 22.2; IR (Neat Film NaCl) 3428, 3041, 2951, 2868, 1472, 1456, 1396, 1370, 1353, 1321, 1259, 1242, 1181, 1117, 1082, 1040, 1015, 950, 911, 862, 809, 793 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{27}O_3$ $[M]^+$: 255.1960; found 255.1951; $[\alpha]_D^{19.9}$ –3.23 ° (*c* 0.99, $CHCl_3$, 88.0% *ee*).

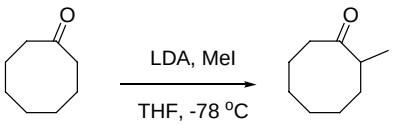
2-[(*S*)-3-(2-Iodo-ethyl)-3-methyl-cyclopent-1-enyl]-2,5,5-trimethyl-[1,3]dioxane (5.126)



PPh_3 (881.3 mg, 3.36 mmol) and imidazole (457.5 mg, 6.72 mmol) were placed in a 25-mL round bottom flask. The flask was evacuated and backfilled with Ar (x 3). CH_2Cl_2 (8.0 mL) was added and the mixture was stirred at 23 °C until all the solids had dissolved (typically within 10 min). The flask was wrapped in aluminum foil and I_2 (869.6 mg, 3.36 mmol) was added. After 10 min stirring, the mixture was cooled to 0 °C by use of an ice/water bath and alcohol **5.125** (571.2 mg, 2.24 mmol) was added as a solution in CH_2Cl_2 (3.0 mL) by use of a syringe. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to 23 °C. After an additional 3 h stirring, hexanes (11 mL) were added and the resulting slurry was filtered through a plug of celite (5 x 1 cm) using hexanes-Et_2O (1:1, 100 mL) as eluent. The filtrate was concentrated under reduced pressure, resuspended in hexanes (50 mL), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (2.0 x 16 cm SiO_2, hexanes → 99:1 → 98:2 → 90:10 Hexanes:Et_2O, dry-loaded using celite) to afford **5.126** 753 mg (2.1 mmol, 92% yield); R_f = 0.71 (7:3 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (s, 1H), 3.50 (app t, 11.5 Hz, 2H), 3.34 (d, *J* = 11.2 Hz, 2H), 3.19-3.06 (m, 2H), 2.38-2.25 (m, 2H), 2.12-2.02 (m, 2H), 1.84 (ddd, *J* = 13.2, 8.8, 5.9 Hz, 1H), 1.67 (ddd, *J* = 13.2, 8.8, 5.6 Hz, 1H), 1.41 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 136.6, 98.6, 71.9, 71.9 (two peaks), 51.2, 46.8, 36.1, 31.4, 29.8, 27.5, 26.4, 22.8, 22.3, 1.1; IR (Neat Film NaCl) 3039, 2956, 2863, 1470, 1450, 1390, 1365, 1315, 1254, 1173, 1119, 1083, 1039, 1011, 944, 915, 866, 814 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{26}O_2I$ $[M+H]^+$: 365.0978; found 365.0980; $[\alpha]_D^{20.3}$ +31.24 ° (*c* 1.03, $CHCl_3$, 88.0% *ee*).

5.8.3 Model Study for the Radical Cyclization

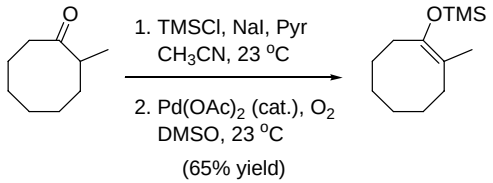
2-Methyl-cyclooctanone [558]



(59% yield)

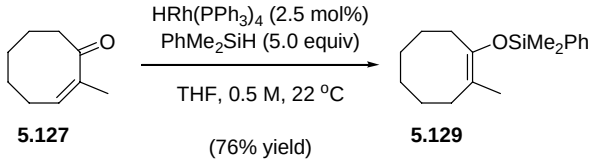
A 250-mL 3-neck flask was charged with diisopropylamine (4.26 g, 5.7 mL, 33.0 mmol), THF (50 mL) was added, and the solution was cooled to 0 °C by use of an ice/water bath. *n*-BuLi (14.8 mL, 33.0 mmol, 2.23 M in hexanes) was added in a dropwise manner keeping the internal temperature below 5 °C. The mixture was stirred for an additional 30 min at 0 °C and then cooled to –78 °C by immersion into a dry ice/acetone bath. Cyclooctanone (3.79g, 30.0 mmol) was dissolved in THF (5.0 mL) and added to the reaction mixture in a dropwise manner over 1 h. After an additional 30 min of stirring at –78 °C, MeI (5.54 g, 2.4 mL, 39.0 mmol) was added in a dropwise manner and the mixture was allowed to warm gradually to 22 °C. After 14 h stirring, the reaction was quenched with saturated aqueous NH_4Cl (25 mL) and diluted with Et_2O (250 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure afford a clear pale yellow oil. The crude oil was purified by flash chromatography (5.0 x 15 cm SiO_2, Hexanes $\rightarrow$ 98:2 Hexanes:Et_2O) to afford 2-methyl-cyclooctanone (2.47 g, 59% yield) as a colorless oil; R_f = 0.79 (9.5:0.5 Hexanes-EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (ddq, *J* = 10.1, 6.9, 3.5 Hz, 1H), 2.43-2.38 (comp. m, 2H), 2.00-1.16 (comp. m, 10H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.5, 45.4, 40.5, 33.2, 27.0, 26.7, 25.8, 24.7, 17.0; IR (Neat Film NaCl) 2925, 2858, 1703, 1463, 1447, 1409, 1375, 1362, 1328, 1197, 1161, 1137, 1096, 1080, 1049, 1008, 962, 933, 905, 858, 830 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{16}O$ $[M]^+$: 140.1201; found 140.1192. Spectral data in accordance with literature values.[559]

Trimethyl-((*E*)-2-methyl-cyclooct-1-enyloxy)-silane[415]



A 100-mL round bottom flask was charged with NaI (2.52 g, 16.8 mmol) and CH_3CN (15 mL). When all the solids had dissolved, 2-methyl-cyclooctanone (1.90 g, 13.6 mmol) in CH_3CN (2.0 mL) and pyridine (1.31 g, 1.33 mL, 16.5 mmol) were added followed by dropwise addition (over 8 min) of TMSCl (1.68 g, 1.96 mL, 15.4 mmol). The resulting pale yellow suspension was stirred at 23 °C for 12 h and then diluted with pentane (40 mL). The biphasic mixture was stirred vigorously for 10 min and the layers were separated. The CH_3CN layer was extracted with pentane (3 x 40 mL). The combined pentane phases were washed with H_2O (2 x 25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude silyl enol ether 2.70 g (12.6 mmol, 93% yield) as a 96:4 mixture (^{1}H NMR) of regioisomers favoring the tetrasubstituted silyl enol ether. An oxygen balloon was affixed to a flask charged with the crude silyl enol ether (2.70 g, 12.6 mmol), $Pd(OAc)_2$ (153 mg, 0.68 mmol, 5 mol%) and DMSO (100 mL). The reaction mixture turned dark and became heterogeneous within 5 min. After 3 h stirring at 23 °C, ^{1}H NMR analysis of an aliquot indicated less than 2% of the undesired isomer. The reaction mixture was poured into a separation funnel containing pentane (100 mL), H_2O (50 mL), and ice (50 g). The layers were separated and the aqueous phase was extracted with pentane (3 x 100 mL). The combined pentane phases were washed with H_2O (2 x 100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. The crude product was purified using flash chromatography (3 x 15 cm MgO_3Si, 98:2 Pentane-Et_2O) to afford trimethyl-((*E*)-2-methyl-cyclooct-1-enyloxy)-silane (1.82 g, 63% yield) as a colorless oil; R_f = 0.78 (9.5:0.5 Hexanes-Et_2O); ^{1}H NMR (500 MHz, C_6D_6) δ 2.24-2.22 (m, 2H), 2.06-2.04 (m, 2H), 1.7 (s, 3H), 1.64-1.59 (m, 2H), 1.52-1.43 (comp. m, 6H), 0.18 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 145.6, 113.3, 32.1, 32.0, 29.3, 29.2, 27.0, 26.8, 16.1, 0.9; IR (Neat Film NaCl) 2956, 2925, 2848, 1680, 1473, 1447, 1372, 1349, 1282, 1269, 1251, 1210, 1186, 1135, 1091, 1052, 1018, 993, 951, 882, 845, 755 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{24}OSi$ $[M]^+$: 212.1596; found 212.1605. Spectral data in accordance with literature values.[415]

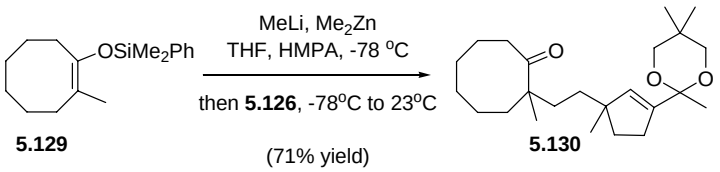
Dimethyl-((*E*)-2-methyl-cyclooct-1-enyloxy)-phenyl-silane (5.129)



5.127 (76% yield) **5.129**

Enone **5.127** (100 mg, 0.724 mmol) was placed in a 1-dram vial. The vial was evacuated and backfilled with N_2 (x 3) and THF (350 μL) was added. $HRh(PPh_3)_4$ (20.9 mg, 0.0181 mmol) was placed in a 10-mL round bottom flask. The flask was evacuated and backfilled with N_2 (3 cycles with 5 min evacuation per cycle) and then THF (1.1 mL) was added. An excess of $PhMe_2SiH$ was placed in a 1-dram vial. The vial was evacuated and backfilled with N_2 (x 3). The required amount of $PhMe_2SiH$ (631 mg, 720 μL, 4.63 mmol) was added to the catalyst mixture by use of a syringe. The resulting clear orange solution was immersed into an oil bath preheated to 30 °C. After 10 min stirring at 30 °C, the solution of enone **5.127** was added by use of positive pressure cannulation. The mixture was stirred at 30 °C for 25 h, allowed to cool to ambient temperature, filtered through a plug of SiO_2 (2 x 1 cm, Et_2O) and concentrated under reduced pressure to afford a pale orange oil. The crude oil was purified by flash chromatography (2 x 16 cm, 99:1 → 98:2 Hexanes-Benzene) to afford **5.129** (150.2 mg, 76% yield) as a colorless oil: R_f = 0.52 (Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.61 (m, 2H), 7.42-7.34 (m, 3H), 2.18-2.14 (m, 2H), 2.06-2.02 (m, 2H), 1.59 (s, 3H), 1.55-1.38 (comp. m, 8H), 0.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 138.7, 133.5, 129.6, 127.9, 113.9, 31.9, 31.6, 29.0, 28.7, 26.8, 26.5, 16.1, -0.4; IR (Neat Film NaCl) 3075, 2951, 2863, 1638, 1468, 1450, 1393, 1370, 1254, 1241, 1179, 1117, 1080, 1037, 1011, 995, 949, 910, 861, 809 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{17}H_{26}OSi$ $[M]^{+\cdot}$: 274.1753; found 274.1752.

2-Methyl-2-(2-[1-methyl-3-(2,5,5-trimethyl-[1,3]dioxan-2-yl)-cyclopent-2-enyl]-ethyl)-cyclooctanone (5.130)

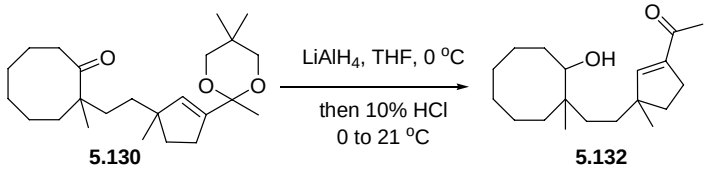


5.129 (71% yield) **5.130**

Silylether **5.129** (39.7 mg, 0.145 mmol) was placed in a 10-mL round bottom flask. The flask was evacuated and backfilled with N_2 (x 3), THF (1.45 mL) was added and the solution was cooled to 0 °C by use of an ice/water bath. MeLi (57 μL, 0.15 mmol, 2.66 M in dimethoxymethane) was added

in a dropwise manner over 5 min. After an additional 1 h stirring at 0 °C, HMPA (260 mg, 252 μL, 1.45 mmol) was added in a dropwise manner over 5 min and then the mixture was cooled to -78 °C by use of an acetone/CO_2 (s) bath. The resulting clear solution mixture was stirred for 10 min followed by addition of Me_2Zn (145 μL, 0.145 mmol, 1.0 M in heptane) in a dropwise manner. After an additional 10 min stirring, alkyl iodide **5.126** (63.4 mg, 0.0174 mmol) in THF (200 μL) was added in a dropwise manner (over 2 min). The mixture was stirred at -78 °C for 1 h and then allowed to warm gradually to ambient temperature. After 21 h stirring at 23 °C, the reaction mixture was diluted with Et_2O and washed with H_2O (10 mL). The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (1 x 19 cm SiO_2, 99:1 → 98:2 → 95:5 → 90:10 Hexanes-Et_2O) to afford **5.130** (43.9 mg, 79% yield) as a 1:1.25 mixture of diastereomers; R_f = 0.70 (3:7 Hexanes-Et_2O); ^{1}H NMR (500 MHz, C_6D_6) δ **major diastereomer:** 5.58 (app t, *J* = 1.7 Hz, 1H), 3.55 (d, *J* = 11.0 Hz, 1H), 3.48 (d, *J* = 11.0 Hz, 1H), 3.31 (d, *J* = 11.0 Hz, 2H), 2.40-2.36 (m, 3H), 2.03 (ddd, *J* = 10.7, 7.1, 3.4 Hz, 1H), 1.81-1.69 (comp. m, 3H), 1.62 (s, 3H), 1.60-1.50 (comp. m, 3H), 1.42-1.22 (comp. m, 8H), 1.19 (s, 3H), 1.18-1.10 (comp. m, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.53 (s, 3H); **minor diastereomer:** 5.56 (app t, *J* = 1.7 Hz, 1H), 3.52 (d, *J* = 11.0 Hz, 1H), 3.48 (d, *J* = 10.7 Hz, 1H), 3.30 (d, *J* = 11.0 Hz, 2H), 2.40-2.36 (m, 3H), 2.02 (ddd, *J* = 10.7, 7.1, 3.4 Hz, 1H), 1.81-1.69 (comp. m, 3H), 1.62 (s, 3H), 1.62 (s, 3H), 1.60-1.50 (comp. m, 3H), 1.42-1.22 (comp. m, 8H), 1.19 (s, 3H), 1.18-1.10 (comp. m, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.52 (s, 3H); Mixture of two diastereomers: ^{13}C NMR (125 MHz, C_6D_6) δ 218.1, 218.1, 142.4, 142.4, 137.9, 137.8, 98.9, 98.9, 71.9, 71.8, 71.8, 71.8, 49.8, 49.8, 48.7, 48.7, 36.9, 36.8, 36.5, 36.5, 35.9, 35.8, 34.6, 34.5, 34.2, 34.1, 31.9, 31.9, 30.4, 30.4, 29.7, 28.1, 28.0, 27.2, 27.1, 26.2, 26.2, 25.3, 25.3, 24.5, 22.9, 22.2, 22.1, 19.2, 19.1; IR (Neat Film NaCl) 2932, 2858, 1698, 1469, 1448, 1396, 1368, 1254, 1239, 1180, 1117, 1083, 1040, 950, 911, 863, 810, 793 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{24}H_{41}O_3$ $[M+H]^+$: 377.3305; found 377.3043.

1-(3-[2-(2-Hydroxy-1-methyl-cyclooctyl)-ethyl]-3-methyl-cyclopent-1-enyl)-ethanone (5.132)

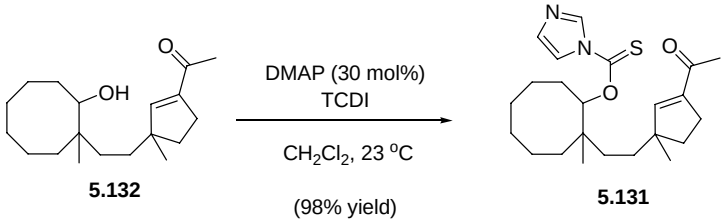


5.130 **5.132**

81% yield

THF (12.5 mL) was added to a 50-mL round bottom flask and cooled to 0 °C by use of an ice/water bath. $LiAlH_4$ (56.9 mg, 1.50 mmol) was added followed by dropwise addition of ketone **5.130** (472 mg, 1.25 mmol) dissolved in THF (4.7 mL). The suspension was stirred at 0 °C for 1.5 h and then the reaction was quenched by dropwise addition of HCl (10 mL, 10% w/w). The suspension was stirred at 0 °C for 2 h, allowed to warm to 23 °C and stirred for an additional 30 min. The reaction mixture was diluted with Et_2O (25 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (2 x 15 cm SiO_2, 7:3 Hexanes-EtOAc) to afford **5.132** (296 mg, 81% yield) as a colorless viscous oil; R_f = 0.22 (7:3 Hexanes-Et_2O); Mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ **major set of diastereomers:** 6.48 (q, *J* = 1.7, 2H), 3.69 (app d, *J* = 7.1 Hz, 1H), 3.68 (app d, *J* = 7.1 Hz, 1H), 2.56-2.52 (comp. m, 4H), 2.30 (s, 6H), 1.95-1.20 (comp. m, 36 H), 1.10 (s, 6H), 1.09 (s, 6H); **minor set of diastereomers:** 6.47 (q, *J* = 2.2 Hz, 2H), 3.76 (app d, *J* = 8.8 Hz, 2H), 2.56-2.52 (comp. m, 4H), 2.30 (s, 6H), 1.95-1.20 (comp. m, 36 H), 0.96 (s, 3H), 0.95 (s, 3H), 0.78 (s, 3H), 0.78 (s, 3H); Mixture of four diastereomers: ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 197.7, 152.9, 152.9, 152.8, 143.4, 143.4, 78.2, 78.2, 77.5, 50.1, 50.1, 50.0, 50.0, 40.3, 40.3, 39.6, 39.6, 36.3, 36.2, 35.3, 35.2, 34.7, 34.7, 34.7, 34.5, 34.5, 33.6, 33.6, 32.3, 32.3, 32.3, 32.1, 29.7, 29.6, 29.1, 29.1, 28.1, 28.1, 27.9, 27.9 26.8, 26.6, 26.6, 26.0, 25.8, 25.6, 25.6, 25.5, 25.4, 23.7, 22.7, 22.2, 22.2, 19.3; IR (Neat Film NaCl) 3468, 3039, 2925, 2853, 1667, 1618, 1468, 1447, 1377, 1365, 1305, 1269, 1204, 1044, 964, 944, 871 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{32}O_2$ $[M]^+$: 292.2402; found 292.2401.

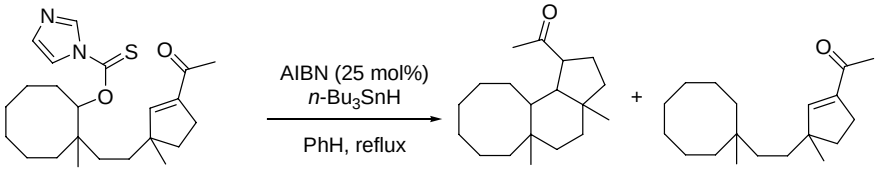
Imidazole-1-carbothioic acid *O*-(2-[2-(3-acetyl-1-methyl-cyclopent-2-enyl)-ethyl]-2-methyl-cyclooctyl) ester (5.131)



5.132 **5.131**

Alcohol **5.132** (66.0 mg, 0.226 mmol) was placed in a 25-mL round bottom flask and dissolved in CH_2Cl_2 (4.7 mL). 4-Dimethylaminopyridine (8.28 mg, 0.068 mmol) and 1,1'-thiocarbonyldiimidazole (201.4 mg, 1.13 mmol) were added and the resulting yellow solution was stirred at 23 °C for 29 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified using flash chromatography (2 x 15 cm SiO_2, 9:1→4:1 Hexanes-EtOAc) to afford **5.131** (89.2 mg, 98% yield) as a sticky colorless oil; R_f = 0.19 (7:3 Hexanes-EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ **major set of diastereomers:** 8.32 (s, 1H), 8.30 (s, 1H), 7.60 (s, 2H), 7.03 (s, 2H), 6.37 (s, 1H), 6.34 (s, 1H), 5.65 (app d, *J* = 8.5 Hz, 2H), 2.63-2.53 (m, 2H), 2.53-2.42 (m, 2H), 2.23 (s, 3H), 2.21 (s, 3H), 2.09-2.03 (m, 2H), 1.84-1.22 (comp. m, 34 H), 1.03 (s, 6H), 1.02 (s, 3H), 1.02 (s, 3H) (two peaks); **minor set of diastereomers:** 8.30 (s, 1H), 8.29 (s, 1 H), 7.59 (s, 1H), 7.55 (s, 1H), 7.03 (s, 2H), 6.45 (s, 1H), 6.44 (s, 1H), 5.77 (app d, *J* = 9.3 Hz, 2H), 2.63-2.53 (m, 2H), 2.53-2.42 (m, 2H), 2.31 (s, 3H), 2.31 (s, 3H), 2.09-2.03 (m, 2H), 1.84-1.22 (comp. m, 34 H), 1.13 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H) ; Mixture of four diastereomers: ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 197.4, 197.4, 184.1, 152.0, 151.9, 151.9, 151.8, 143.8, 143.7, 143.6, 143.6, 136.8, 136.7, 130.9, 130.9, 118.0, 117.9, 117.8, 91.7, 91.6, 91.3, 91.2 50.0, 49.9, 49.7, 49.7, 40.2, 40.2, 39.9, 39.9, 36.3, 36.1, 36.1, 36.0, 35.2, 34.8, 34.7, 34.6, 34.5, 34.4, 32.5, 32.4, 32.3, 31.3, 30.5, 30.5, 29.9, 29.8, 29.7, 29.6, 28.7, 28.6, 27.6, 27.4, 27.4, 26.8, 26.8, 26.7, 26.4, 26.2, 25.7, 25.6, 25.3, 25.3, 25.1, 25.1, 23.3, 23.3, 22.6, 22.6, 22.1, 22.1, 21.5, 21.4; IR (Neat Film NaCl) 3158, 3121, 2930, 2853, 1664, 1618, 1530, 1460, 1383, 1328, 1282, 1228, 1099, 1037, 1013, 967, 889, 871, 830, 734; HRMS (EI+) *m/z* calc'd for $C_{23}H_{34}N_2O_2S$ $[M]^+$: 402.2341; found 402.2354.

1-(3*a*,5*a*-Dimethyl-tetradecahydro-cycloocta[*e*]inden-1-yl)-ethanone (5.131) and 1-(3-methyl-3-[2-(1-methyl-cyclooctyl)-ethyl]-cyclopent-1-enyl)-ethanone (5.133)



5.131 **5.134** 83% yield **5.133** 9% yield

Thiocarbonate **5.131** (41.2 mg, 0.102 mmol) was placed in a 50-mL round bottom 2-neck flask fitted with a condenser, benzene (18.4 mL) was added, and the solution was sparged with N_2 for 1 h. The reaction mixture was immersed into an oil bath and heated to reflux (oil bath at 85 °C. AIBN (4.19 mg, 0.026 mmol) was placed in a 10-mL flask. The flask was evacuated and backfilled with N_2 (x 3). Benzene (2.0 mL, sparged with N_2 for 1 h prior to use) was added followed by *n*-Bu_3SnH (59.4 mg, 54 μL, 0.204 mmol). The solution was added dropwise to the reaction mixture over 5 h by use of syringe pump. The mixture was stirred for an additional 12 h at reflux, allowed to cool to ambient temperature, and concentrated under reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography (1 x 15 cm, SiO_2 impregnated with $AgNO_3$, Hexanes) to afford a mixture of diastereomers of the desired ketone **5.134** (23.4 mg, 83% yield) and deoxygenated product **5.133** (2.5 mg, 9% yield) (ratio judged by ^{1}H NMR). Samples of sufficient purity for NMR were obtained by flash chromatography (1 x 10 cm SiO_2, Hexanes → 99:1 → 98:1 Hexanes-Et_2O) and subsequent preparative TLC (20 x 20 cm, compound applied 2 cm from bottom, Toluene, developed x 3) of the fractions containing mainly the desired set of diastereomers.

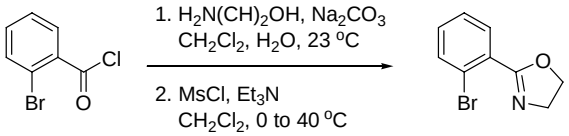
Major diastereomer (5.134): R_f = 0.52 (4:1 Hexanes-Et_2O); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.27 (ddd, *J* = 10.8, 7.3, 7.3 Hz, 1H), 2.38 (app dt, *J* = 7.0, 1.2 Hz, 1H), 2.27-2.22 (m, 1H), 2.20 (s, 3H), 1.78-1.74 (m, 2H), 1.67-1.10 (comp. m, 12H), 0.98 (s, 3H), 0.96 (s, 3H), 0.89-0.81 (comp. m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 56.9, 49.5, 42.7, 42.0, 37.9, 36.4, 34.6, 31.7, 31.6, 31.5, 30.9, 30.4, 26.8, 26.0, 25.6, 23.3, 23.0, 22.4; IR (Neat Film NaCl) 2920, 2853, 1708, 1460, 1377, 1199, 1179 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{32}O$ $[M]^+$: 276.2453; found 276.2450.

Minor set of diastereomers (5.134): R_f = 0.58 (4:1 Hexanes-Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (ddd, *J* = 10.0, 8.3, 5.6 Hz, 1H), 2.71-2.64 (m, 1H), 2.35 (app t, *J* = 7.3 Hz, 1H), 2.17 (s, 3H),

2.16 (s, 3H), 2.07-1.85 (comp. m, 4H), 1.76-1.06 (comp. m, 33H), 1.04 (s, 3H), 1.03 (s, 3H), 1.00-0.82 (comp. m, 6H), 0.77 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 211.2, 58.8, 55.9, 44.6, 44.5, 41.3, 40.9, 40.9, 39.6, 36.4, 35.2, 34.6, 34.0, 33.1, 32.1, 32.0, 30.7, 29.9, 29.9, 29.5, 29.4, 29.2, 29.0, 28.8, 28.7, 27.9, 27.2, 26.4, 26.2, 25.8, 25.4, 24.6, 24.5, 24.3, 22.8, 22.1, 19.8; IR (Neat Film NaCl) 2919, 2848, 1737, 1711, 1460, 1383, 1352, 1261, 1173 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{32}O$ $[M]^+$: 276.2453; found 276.2441.

5.8.4 Ligand Synthesis

2-(2-Bromo-phenyl)-4,5-dihydro-oxazole



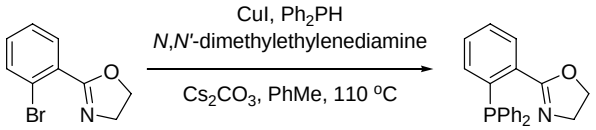
(64% yield)

Ethanolamine (1.34 g, 1.32 mL, 21.9 mmol) was placed in a 250-mL round bottom flask and dissolved in CH_2Cl_2 (60 mL) and a solution of Na_2CO_3 (5.80 g, 54.7 mmol) in H_2O (45 mL) was added. To the vigorously stirred biphasic system was added neat 2-bromobenzoyl chloride (4.00 g, 2.38 mL, 18.2 mmol) dropwise via syringe. The reaction flask was capped with a yellow plastic stopper and stirred for 7.5 h at 23 °C. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white solid. The crude product was dissolved in CH_2Cl_2 (50 mL) and hexanes (10 mL) were added. The solution was concentrated to ~ 25 mL under reduced pressure resulting in precipitation of the desired amide 4.02 g (16.4 mmol, 90% yield) as a white solid.

The above amide (2.0 g, 8.2 mmol) was placed in a 100-mL round bottom flask equipped with a reflux condenser and dissolved in CH_2Cl_2 (62 mL). Et_3N (2.49 g, 3.43 mL, 24.5 mmol) was added and the solution was cooled to 0 °C by use of an ice/water bath followed by dropwise addition of MsCl (1.41 g, 952 μL, 12.3 mmol). The reaction mixture was stirred at 0 °C for 30 min, then transferred to an oil bath and heated to 40 °C. After 5 h stirring, the resulting yellow solution was allowed to cool to ambient temperature, diluted with CH_2Cl_2 (25 mL), washed with H_2O (2 x 25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a

thick, pale yellow oil. The crude oil was purified by flash chromatography (5 x 10 cm SiO_2, 6:2:2 Hexanes-EtOAc-Toluene) to afford 2-(2-bromo-phenyl)-4,5-dihydro-oxazole (1.31 g, 71% yield); R_f = 0.45 (9.0:1.0 $CHCl_3$-MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 2.0 Hz 1H), 7.65 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.35 (app dt, *J* = 7.6, 1.2 Hz, 1H), 7.29 (app dt, *J* = 7.6, 1.7 Hz, 1H), 4.46 (t, *J* = 9.6 Hz, 2H), 4.12 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 134.1, 131.8, 131.5, 129.8, 127.2, 122.0, 67.8, 55.5; IR (Neat Film NaCl) cm^{-1} 3390, 3070, 2966, 2904, 2868, 1729, 1646, 1589, 1432, 1362, 1328, 1272, 1243, 1093, 1026, 938: HRMS (EI+) *m*/*z* calc'd for C_9H_8BrNO $[M]^+$: 224.9789; found 224.9779.

2-(2-Diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole

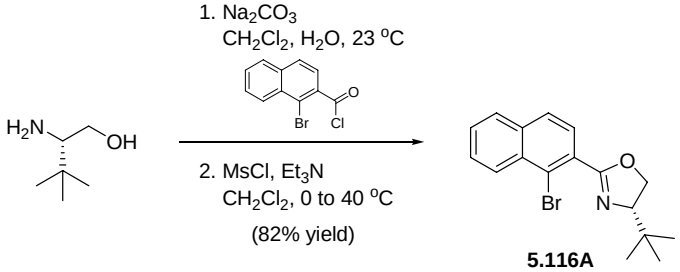


(86% yield)

A 250-mL Schlenk flask was charged with CuI (66.7 mg, 0.35 mmol), Ph_2PH (4.12g, 3.85 mL, 22.1 mmol) and then *N*,*N*'-dimethylethylenediamine (156 mg, 191 μL, 1.77 mmol) followed by toluene (18 ml). The solution was stirred at 23 °C for 20 min. 2-(2-Bromo-phenyl)-4,5-dihydro-oxazole (4.0 g, 17.7 mmol) was azeotroped with toluene (2 x 5 ml) under reduced pressure, then dissolved in toluene (18 mL) and transferred quantitatively to the Schlenk flask by use of positive pressure cannulation. Cs_2CO_3 (8.65 g, 26.5 mmol) was added in one portion, the flask was evacuated, and backfilled with Ar (x 3). The Teflon valve was sealed and the yellow heterogeneous reaction mixture was placed in an oil bath, heated to 110 °C, and stirred vigorously. After 20 h stirring at 110 °C, the mixture was allowed to cool to ambient temperature and filtered through a pad of celite using CH_2Cl_2 (2 x 50 mL). The filtrate was concentrated under reduced pressure to afford a clear orange oil. The crude oil was flushed through a plug of silica gel (5.0 x 10 cm SiO_2, hexanes → 9:1 dichloromethane:Et_2O) to afford 2-(2-diphenylphosphanyl-phenyl)-4,5-dihydro-oxazole (5.03 g, 86% yield) as a colorless viscous oil that crystallized upon standing; R_f = 0.50 (7:3 Hexanes-EtOAc); ^{31}P NMR (121 MHz, $CDCl_3$) δ -3.99 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.6, 3.4 Hz, 1H), 7.37-7.26 (comp. m, 12H), 6.89 (dd, *J* = 4.1, 7.6 Hz, 1H), 4.08 (t, *J* = 9.5 Hz, 2H), 3.78 (t, *J* = 9.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (d, J_{CP} = 2.8 Hz), 139.1 (d, J_{CP} = 24.9 Hz), 138.0 (d, J_{CP} = 11.5 Hz), 134.1 (d, J_{CP} = 20.7 Hz), 133.7 (d, J_{CP} = 1.8 Hz), 131.9 (d, J_{CP} = 18.9

Hz), 130.5, 129.9 (d, J_{CP} = 2.8 Hz), 128.7, 128.5 (d, J_{CP} = 7.4 Hz), 128.1, 67.2, 55.0; IR (Neat Film NaCl) 3053, 3000, 2971, 2901, 2876, 1650, 1585, 1562, 1478, 1434, 1354, 1326, 1248, 1133, 1089, 1070, 1041, 974, 942, 898, 743 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{21}H_{19}NOP$ $[M+H]^+$: 332.1204; found 332.1218; mp = 99-101 °C.

(*S*)-2-(1-Bromo-naphthalen-2-yl)-4-*tert*-butyl-4,5-dihydro-oxazole (5.116A)



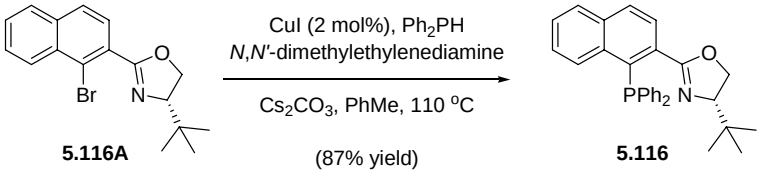
5.116A

(*S*)-*tert*-Leucinol (1.02 g, 8.66 mmol) was placed in a 250-mL round bottom flask and dissolved in CH_2Cl_2 (14.0 mL). Na_2CO_3 (2.75 g, 26.0 mmol) was added as a solution in H_2O (27.0 mL). To the biphasic mixture was added a solution of 1-bromonaphthalene-2-carbonyl chloride (2.68 g, 9.96 mmol) in CH_2Cl_2 (15.0 mL). The biphasic system was stirred vigorously at 23 °C for 9.5 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were stirred with KOH (10 mL, 10 mmol, 1.0 N in MeOH) for 30 min then transferred to a separation funnel. H_2O (10 mL) was added and the mixture was neutralized with HCl (6.0 M, in H_2O). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired amide as a pale yellow solid 3.03 g (9.96 mmol, quantitative).

The above amide (3.03 g, 9.96 mmol) was placed in a 100-mL 3-neck round bottom flask fitted with a condenser and dissolved in CH_2Cl_2 (43.3 mL). The solution was cooled to 0 °C by use of an ice/water bath and Et_3N (2.10 g, 2.90 mL, 20.8 mmol) was added followed by dropwise addition of methanesulfonyl chloride (1.14 g, 0.77 mL, 9.96 mmol). Following consumption of the starting material as indicated by TLC (typically 15 min stirring), the reaction mixture was warmed to 40 °C in a water bath. After 21 h stirring at 40 °C the mixture was allowed to cool to room temperature and saturated aqueous $NaHCO_3$ was added. The biphasic system was stirred vigorously for 5 min and then the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under

reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography (SiO_2 3 x 15 cm, 9:1 Hexanes-EtOAc) to afford **5.116A** (2.36 g, 82% yield over two steps) as a pale yellow oil that solidifies when placed in a –20 °C freezer; R_f = 0.73 (9.0:1.0 $CHCl_3$-MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.85-7.81 (m, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.60 (app dt, *J* = 8.2, 1.3 Hz, 1H), 7.56 (app dt, *J* = 6.9, 1.3 Hz, 1H), 4.46 (dd, *J* = 8.5, 10.4 Hz, 1H), 4.33 (dd, 8.5, 8.0 Hz, 1H), 4.17 (dd, 8.2, 10. 4 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 134.9, 132.3, 128.8, 128.3, 128.3, 128.0, 127.8, 127.7, 126.9, 123.2, 76.9, 69.2, 34.1, 26.1; IR (Neat Film NaCl) 3065, 2956, 2899, 2863, 1667, 1620, 1594, 1556, 1499, 1476, 1463, 1393, 1372, 1362, 1339, 13212, 1300, 1238, 1264, 1210, 1161, 1104, 1024, 977, 956, 920, 817, 752 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{18}ONBr$ $[M]^+$: 331.0572; found 331.0583; $[\alpha]_D^{20.0}$ –63.95 ° (*c* 0.92, $CHCl_3$); mp = 66-68 °C.

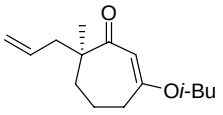
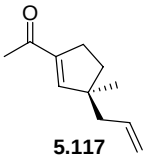
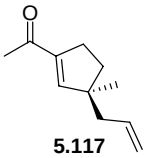
(*S*)-4-*tert*-Butyl-2-(1-diphenylphosphanyl-naphthalen-2-yl)-4,5-dihydro-oxazole (5.116)



Prepared by the typical method employing **5.116A** (830.6 mg, 2.50 mmol). After 24 h stirring, the reaction mixture was filtered through a plug of celite washing with CH_2Cl_2 (2 x 25 mL) and concentrated under reduced pressure. The crude oil was flashed through a short path of silica (2.5 x 8 cm SiO_2, Hexanes → 9:1 dichloromethane:Et_2O) to afford a bright yellow oil containing the desired product. The oil was purified by flash chromatography (2.5 x 25 cm SiO_2, 19:1 Hexanes-Acetone and then 2.5 x 21 cm SiO_2, 9:1 → 6:1 Hexanes-EtOAc) to afford **5.116** (950.8 mg, 87% yield) as a bright yellow foam; ^{31}P NMR (121 MHz, $CDCl_3$) δ -9.33(s); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.72 (dd, *J* = 8.3, 2.9 Hz, 1H), 7.45 (app dt, *J* = 7.8, 1.7 Hz, 2H); 7.41-7.38 (m, 3H), 7.29-7.22 (comp. m, 6H). 7.16 (ddd, *J* = 8.3, 6.9, 1.0 Hz, 1H), 4.17-4.15 (m, 2H), 3.91 (dd, *J* = 9.8, 8.8 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (d, J_{CP} = 5.1 Hz), 137.5 (d, J_{CP} = 33.1 Hz), 136.8, (d, J_{CP} = 14.7 Hz), 136.5 (d, J_{CP} = 14.7), 134.9, 134.7 (d, J_{CP} = 33.6 Hz), 133.1 (d, J_{CP} = 26.7 Hz), 132.2 (d, J_{CP} = 17.5 Hz), 132.1 (d, J_{CP} = 17.5 Hz), 131.5 (d, J_{CP} = 0.9 Hz), 129.1 (d, J_{CP} = 7.4 Hz), 129.0, 128.4 (d, J_{CP} = 6.0 Hz), 127.8 (d, J_{CP} = 8.3 Hz), 126.6 (d, J_{CP} = 8.7 Hz), 126.4 (d, J_{CP} = 40.5 Hz), 76.8, 69.0, 34.1, 26.3; IR (Neat Film

NaCl) 3054, 2954, 2867, 1665, 1584, 1478, 1434, 1364, 1244, 1094, 1026, 986, 962, 922, 824 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{29}H_{28}NOP$ $[M]^+$: 437.1908; found 437.1908; $[\alpha]_D^{26.1}$ –38.2 ° (*c* 1.59, *n*-Hexane).

Table 5.5 Methods for the determination of enantiomeric excess.

entry	product	assay conditions[a]	retention time of major isomer (min)	retention time of minor isomer (min)	*%ee*
1	 **5.51**	HPLC Chiralcel OD-H 1% IPA in *n*-hexane isocratic, 1.0 mL/min	6.30	7.26	88
2	 **5.117**	GC G-TA 80 °C isotherm	54.98	61.35	88
3	 **5.117**	GC G-TA 80 °C isotherm	54.74	60.24	98

[a] Suitable assay conditions were developed utilizing racemic material.

6 Concluding Remarks

The importance of transition metal-catalyzed C-C bond formation within the area of synthetic organic chemistry can hardly be overestimated. The development of transition-metal-catalyzed regio-, chemo-, and enantioselective C-C bond forming reactions continues to be a central research area, which has a widespread impact on organic synthesis. The ability to construct C-C bonds by novel and more efficient means greatly influences our ability to construct complex molecules. The present work has evolved around four projects within the general area of organic synthesis and method development. Crucial to these projects was the development or application of ruthenium- or palladium-catalyzed C-C bond forming reactions.

A concise synthesis of (+)-castanospermine starting from methyl α-D-glucopyranoside has been developed. The octahydroindolizidine skeleton of (+)-castanospermine was constructed be sequential use of a medium ring metathesis reaction, a diastereoselective epoxidation, and a strain-releasing transannular cyclization. The second project has culminated in an efficient synthetic strategy to the (–)-pladienolide B core. The synthesis relied on chiral auxiliary-mediated aldol addition and Sharpless asymmetric dihydroxylation to install the three oxygen substituted stereocenters of the macrocycle. (*E*)-Selective cross metathesis combined with Yamaguchi-macrolactonization afforded the 12-membered lactone. This approach constitutes a flexible and excellent starting point for future analog synthesis of the very promising anticancer lead structure pladienolide B. The third project was directed toward the development of an efficient and atom-economical protocol to directly alkylate the 3-position of oxindoles utilizing alcohols. This was achieved employing cheap and commercially available [$RuCl_3 \cdot xH_2O$] as catalyst. The reaction was highly selective for the formation of C(3) substituted oxindoles. Moreover, this transformation was tolerant to a wide range of functional groups and could be applied to a range of different alcohols. The final project was concerned with synthetic studies toward the sesterterpenoid variecolin. Synthetic routes to two main fragments were developed. Key to these achievements was the implementation of the tandem Wolff-Cope rearrangement and the palladium-catalyzed enantioselective decarboxylative allylation. In addition model studies revealed that these fragments could be convergently combined through a 1,4-hydrosilylation-alkylation sequence followed by conjugate radical cyclization.

7 Abbreviations

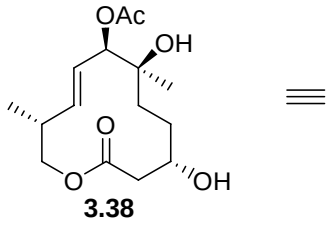
Ac	Acetyl
acac	Acetylacetonate
AD	Asymmetric dihydroxylation (Sharpless)
AIBN	2,2'-Azobisisobutyronitrile
aq	Aqueous
app	Apparent (NMR)
AQN	Anthraquinone
BHT	2,6-Di-*tert*-butyl-4-methylphenol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Base pair
bp	Boiling point
br s	Broad singlet (NMR)
i-Bu	*iso*-Butyl
n-Bu	*normal*-Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
Caltech	California Institute of Technology
CAN	Cerium(IV) ammonium nitrate
cat	Catalyst / catalytic amount
Cbz	Benzyloxocarbonyl
CCR5	Chemokine receptor 5
CD4	Cluster of differentiation 4
CM	Cross metathesis
CNS	Central nervous system
cod	1,5-Cyclooctadiene
Con A	Concanavalin A
Cp*	Pentamethylcyclopentadienyl
*m*CPBA	*meta*-Chloroperbenzoic acid
CSA	Camphorsulfonic acid
CXCR5	CXC chemokine receptor 5
Cy	Cyclohexyl
d	Doublet (NMR)
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DEIPS	Diethylisopropylsilyl
DHQD	Dihydroquinidine
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine, Hünigs base
DIPHOS	Dithylenebis(diphenylphosphine)
(+)-DIPT	(+)-Diisopropyl tartrate
dmdba	Bis(3,5-dimethoxybenzylidene)-acetone
DMAC	Dimethyl acetamide
DMAP	4-(Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone

DMS	Dimethyl sulfide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
DTS	Diverted total synthesis
E	Entgegen
EC_{50}	Half maximal effective concentration
EDTA	Ethylenediamine tetraacetic acid
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron-withdrawing group
FOS	Function oriented synthesis
GC	Gas chromatography
h	Hour(s)
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond connectivity
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
$5\text{-}HT_7$	5-Hydroxytryptamine receptor 7
IC_{50}	Half maximal inhibitory concentration
IDCP	Iodonium dicollidine perchlorate
IR	Infrared
KDA	Potassium diisopropylamide
KHMDS	Potassium bis(trimethylsilyl) -amide
L	Ligand
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl) -amide
m	*meta*
m	Mulitplet (NMR)
M	Molar
MAPh	Methylaluminum bis(2,6-diphenyloxide)
Me	Methyl
Mes	Mesityl
MIT	Massachusetts Institute of Technology
MOM	Methoxymethyl
Ms	Methanesulfonyl
MS	Mass spectrometry
MS	Molecular sieves
MSH	*ortho*-Mesitylenesulfonyl-hydroxylamine
NaHMDS	Sodium bis(trimethylsilyl) -amide
NBD	Norbornadiene
NHC	*N*-Heterocyclic carbene
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	*Ortho*
p	*Para*
PCC	Pyridinium chlorochromate
Pf	9-Phenylfluorenyl
Pg	Protection group

Ph	Phenyl
PHAL	Phtalazine
PHOX	Phosphinooxazoline
Piv	Pivaloyl
PKC	Protein kinase C
PLAP	Placental alkaline phosphatase
PMB	*para*-Methoxybenzyl
pmdba	bis(4-methoxy-benzylidene)acetone
PP	Diphosphate
PPTS	Pyridinium *para*-toluenesulfonate
i-Pr	*iso*-Propyl
pyr	Pyridine
q	Quartet (NMR)
R_f	Retention factor
RCM	Ring-closing olefin metathesis
RNA	Ribonucleic acid
ROMP	Ring-opening olefin metathesis polymerization
s	Singlet (NMR)
S_N2	Bimolecular nucleophilic substitution
t	Triplet (NMR)
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TCDI	1,1'-Thiocarbonyldiimidazole
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
o-Tol	*ortho*-Tolyl
TPAP	Tetra-*N*-propylammonium perruthenate
Tr	Trityl, triphenylmethyl
Ts	*p*-Toluenesulfonyl, tosyl
X	Halogen, oxygen or sulfur
Xantphos	9,9-Dimethyl-4,5-bis(diphenyl-phosphino)xanthene
Xphos	2',4',6'-Triisopropyl-2-dicyclohexylphosphinobiphenyl
UHP	Urea hydrogen peroxide
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
Z	Zusammen

8 Appendix A – X-ray Structure of 3.38

Contents:



3.38

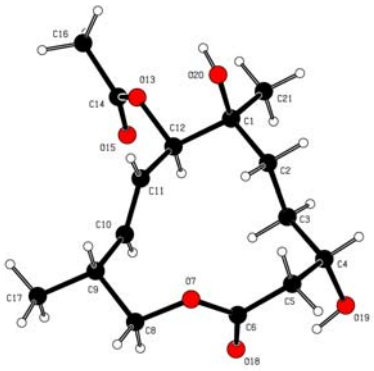


Table 1. Crystal data and structure refinement for 3.38.

Empirical formula	$C_{15}H_{24}O_6$	
Formula weight	300.34	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 5.563(2) Å	α = 90°
	b = 9.190(2) Å	β = 90°
	c = 30.584(6) Å	γ = 90°
Volume	1563.6(7) $Å^3$	
Z	4	
Density (calculated)	1.276 g/cm^3	
Absorption coefficient	0.816 mm^{-1}	
F(000)	648	
Crystal size	0.31 x 0.15 x 0.14 mm^3	
Theta range for data collection	2.89 to 68.23°	
Index ranges	-6<=h<=6, -10<=k<=11, -36<=l<=36	
Reflections collected	22545	
Independent reflections	2844 [R(int) = 0.0325]	
Completeness to theta = 68.23°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8944 and 0.7861	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2844 / 0 / 201	
Goodness-of-fit on F^2	1.087	
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0673	
R indices (all data)	R1 = 0.0278, wR2 = 0.0679	
Absolute structure parameter	0.06(13)	
Largest diff. peak and hole	0.146 and -0.297 $e.Å^{-3}$	

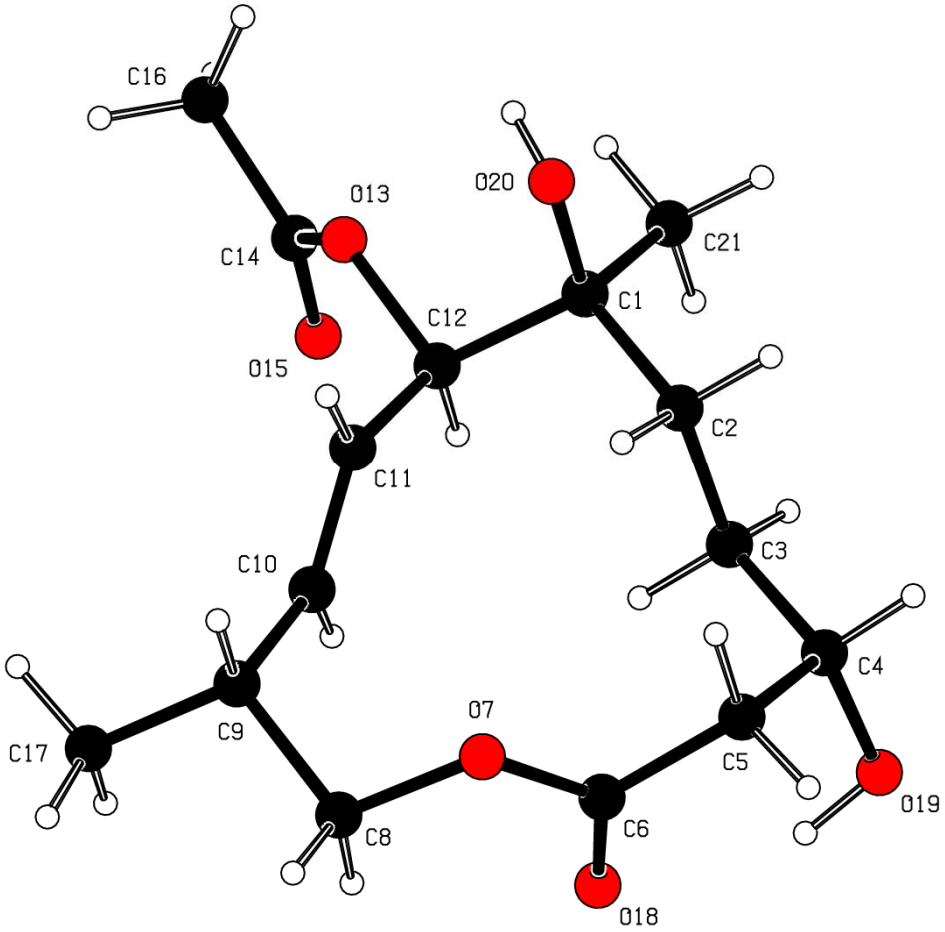

C16
O13
O20
C14
C21
C1
C12
O15
C2
C11
C3
C10
C4
O7
C9
C17
C5
O19
C8
C6
O18

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 3.38. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9576(2)	1969(1)	8632(1)	16(1)
C(2)	9430(2)	924(1)	8244(1)	18(1)
C(3)	7046(2)	917(1)	7996(1)	18(1)
C(4)	7046(2)	-148(1)	7611(1)	19(1)
C(5)	7448(2)	-1744(1)	7748(1)	18(1)
C(6)	5551(2)	-2217(1)	8067(1)	17(1)
O(7)	6469(2)	-2885(1)	8418(1)	19(1)
C(8)	4827(2)	-3248(1)	8768(1)	21(1)
C(9)	5590(2)	-2434(1)	9182(1)	18(1)
C(10)	5718(2)	-826(1)	9091(1)	17(1)
C(11)	7680(2)	-6(1)	9111(1)	18(1)
C(12)	7687(2)	1564(1)	8983(1)	16(1)
O(13)	8339(2)	2430(1)	9371(1)	18(1)
C(14)	6730(2)	3351(1)	9538(1)	17(1)
O(15)	4707(2)	3517(1)	9399(1)	23(1)
C(16)	7739(3)	4152(1)	9924(1)	24(1)
C(17)	3753(2)	-2775(1)	9542(1)	22(1)
O(18)	3426(2)	-1973(1)	8017(1)	24(1)
O(19)	4865(2)	-21(1)	7366(1)	25(1)
O(20)	11926(2)	1728(1)	8809(1)	20(1)
C(21)	9320(2)	3556(1)	8496(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for 3.38.

C(1)-O(20)	1.4314(15)	C(1)-C(2)-H(2B)	108.3
C(1)-C(21)	1.5233(17)	H(2A)-C(2)-H(2B)	107.4
C(1)-C(2)	1.5307(16)	C(2)-C(3)-C(4)	112.61(10)
C(1)-C(12)	1.5458(16)	C(2)-C(3)-H(3A)	109.1
C(2)-C(3)	1.5277(17)	C(4)-C(3)-H(3A)	109.1
C(2)-H(2A)	0.9900	C(2)-C(3)-H(3B)	109.1
C(2)-H(2B)	0.9900	C(4)-C(3)-H(3B)	109.1
C(3)-C(4)	1.5302(16)	H(3A)-C(3)-H(3B)	107.8
C(3)-H(3A)	0.9900	O(19)-C(4)-C(3)	110.53(10)
C(3)-H(3B)	0.9900	O(19)-C(4)-C(5)	110.07(10)
C(4)-O(19)	1.4315(16)	C(3)-C(4)-C(5)	113.53(9)
C(4)-C(5)	1.5416(17)	O(19)-C(4)-H(4)	107.5
C(4)-H(4)	1.0000	C(3)-C(4)-H(4)	107.5
C(5)-C(6)	1.5017(17)	C(5)-C(4)-H(4)	107.5
C(5)-H(5A)	0.9900	C(6)-C(5)-C(4)	110.49(10)
C(5)-H(5B)	0.9900	C(6)-C(5)-H(5A)	109.6
C(6)-O(18)	1.2126(16)	C(4)-C(5)-H(5A)	109.6
C(6)-O(7)	1.3372(15)	C(6)-C(5)-H(5B)	109.6
O(7)-C(8)	1.4461(15)	C(4)-C(5)-H(5B)	109.6
C(8)-C(9)	1.5320(17)	H(5A)-C(5)-H(5B)	108.1
C(8)-H(8A)	0.9900	O(18)-C(6)-O(7)	123.98(11)
C(8)-H(8B)	0.9900	O(18)-C(6)-C(5)	123.31(11)
C(9)-C(10)	1.5056(17)	O(7)-C(6)-C(5)	112.67(10)
C(9)-C(17)	1.5336(17)	C(6)-O(7)-C(8)	117.27(10)
C(9)-H(9)	1.0000	O(7)-C(8)-C(9)	108.95(10)
C(10)-C(11)	1.3281(18)	O(7)-C(8)-H(8A)	109.9
C(10)-H(10)	0.9500	C(9)-C(8)-H(8A)	109.9
C(11)-C(12)	1.4956(17)	O(7)-C(8)-H(8B)	109.9
C(11)-H(11)	0.9500	C(9)-C(8)-H(8B)	109.9
C(12)-O(13)	1.4752(13)	H(8A)-C(8)-H(8B)	108.3
C(12)-H(12)	1.0000	C(10)-C(9)-C(8)	109.80(10)
O(13)-C(14)	1.3328(15)	C(10)-C(9)-C(17)	111.41(10)
C(14)-O(15)	1.2121(17)	C(8)-C(9)-C(17)	108.05(10)
C(14)-C(16)	1.5006(17)	C(10)-C(9)-H(9)	109.2
C(16)-H(16A)	0.9800	C(8)-C(9)-H(9)	109.2
C(16)-H(16B)	0.9800	C(17)-C(9)-H(9)	109.2
C(16)-H(16C)	0.9800	C(11)-C(10)-C(9)	125.99(11)
C(17)-H(17A)	0.9800	C(11)-C(10)-H(10)	117.0
C(17)-H(17B)	0.9800	C(9)-C(10)-H(10)	117.0
C(17)-H(17C)	0.9800	C(10)-C(11)-C(12)	122.53(11)
O(19)-H(19)	0.863(19)	C(10)-C(11)-H(11)	118.7
O(20)-H(20)	0.790(19)	C(12)-C(11)-H(11)	118.7
C(21)-H(21A)	0.9800	O(13)-C(12)-C(11)	108.01(9)
C(21)-H(21B)	0.9800	O(13)-C(12)-C(1)	105.15(9)
C(21)-H(21C)	0.9800	C(11)-C(12)-C(1)	114.60(10)
O(20)-C(1)-C(21)	109.70(10)	O(13)-C(12)-H(12)	109.6
O(20)-C(1)-C(2)	104.10(9)	C(11)-C(12)-H(12)	109.6
C(21)-C(1)-C(2)	112.50(10)	C(1)-C(12)-H(12)	109.6
O(20)-C(1)-C(12)	108.81(9)	C(14)-O(13)-C(12)	119.04(9)
C(21)-C(1)-C(12)	110.93(10)	O(15)-C(14)-O(13)	124.72(11)
C(2)-C(1)-C(12)	110.53(9)	O(15)-C(14)-C(16)	124.11(12)
C(3)-C(2)-C(1)	115.75(10)	O(13)-C(14)-C(16)	111.16(11)
C(3)-C(2)-H(2A)	108.3	C(14)-C(16)-H(16A)	109.5
C(1)-C(2)-H(2A)	108.3	C(14)-C(16)-H(16B)	109.5
C(3)-C(2)-H(2B)	108.3	H(16A)-C(16)-H(16B)	109.5

C(14)-C(16)-H(16C)	109.5	H(17B)-C(17)-H(17C)	109.5
H(16A)-C(16)-H(16C)	109.5	C(4)-O(19)-H(19)	106.3(12)
H(16B)-C(16)-H(16C)	109.5	C(1)-O(20)-H(20)	108.7(13)
C(9)-C(17)-H(17A)	109.5	C(1)-C(21)-H(21A)	109.5
C(9)-C(17)-H(17B)	109.5	C(1)-C(21)-H(21B)	109.5
H(17A)-C(17)-H(17B)	109.5	H(21A)-C(21)-H(21B)	109.5
C(9)-C(17)-H(17C)	109.5	C(1)-C(21)-H(21C)	109.5
H(17A)-C(17)-H(17C)	109.5	H(21A)-C(21)-H(21C)	109.5
		H(21B)-C(21)-H(21C)	109.5

Symmetri transformations used to generate equivalent atoms.

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 3.38. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	13(1)	17(1)	19(1)	-1(1)	-1(1)	0(1)
C(2)	17(1)	18(1)	18(1)	-1(1)	1(1)	0(1)
C(3)	20(1)	17(1)	19(1)	0(1)	-2(1)	1(1)
C(4)	21(1)	21(1)	16(1)	-1(1)	-2(1)	-1(1)
C(5)	19(1)	18(1)	17(1)	-3(1)	-1(1)	1(1)
C(6)	20(1)	13(1)	19(1)	-3(1)	-2(1)	3(1)
O(7)	19(1)	20(1)	18(1)	0(1)	0(1)	2(1)
C(8)	24(1)	19(1)	21(1)	1(1)	2(1)	-3(1)
C(9)	18(1)	17(1)	20(1)	2(1)	1(1)	2(1)
C(10)	18(1)	19(1)	15(1)	0(1)	1(1)	3(1)
C(11)	18(1)	20(1)	15(1)	-1(1)	-2(1)	3(1)
C(12)	15(1)	18(1)	15(1)	-4(1)	-2(1)	0(1)
O(13)	18(1)	20(1)	17(1)	-5(1)	-3(1)	1(1)
C(14)	22(1)	14(1)	17(1)	3(1)	0(1)	-2(1)
O(15)	21(1)	22(1)	26(1)	-6(1)	-3(1)	3(1)
C(16)	28(1)	22(1)	22(1)	-5(1)	-4(1)	1(1)
C(17)	25(1)	18(1)	24(1)	2(1)	3(1)	1(1)
O(18)	18(1)	26(1)	29(1)	4(1)	-1(1)	3(1)
O(19)	30(1)	23(1)	22(1)	1(1)	-10(1)	-1(1)
O(20)	14(1)	21(1)	24(1)	-7(1)	-4(1)	1(1)
C(21)	22(1)	19(1)	22(1)	-1(1)	-1(1)	0(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for 3.38.

	x	y	z	U(eq)
H(2A)	10728	1174	8036	21
H(2B)	9745	-75	8351	21
H(3A)	6715	1909	7885	22
H(3B)	5736	650	8200	22
H(4)	8401	132	7413	23
H(5A)	7395	-2377	7486	21
H(5B)	9055	-1846	7884	21
H(8A)	4855	-4311	8821	25
H(8B)	3170	-2967	8686	25
H(9)	7210	-2787	9276	22
H(10)	4262	-355	9011	21
H(11)	9135	-433	9211	21
H(12)	6050	1852	8879	19
H(16A)	6967	5107	9947	36
H(16B)	9475	4280	9885	36
H(16C)	7435	3592	10191	36
H(17A)	4299	-2353	9819	33
H(17B)	3596	-3831	9574	33
H(17C)	2192	-2357	9463	33
H(19)	3770(30)	-470(20)	7515(6)	33(5)
H(20)	12190(30)	2330(20)	8988(6)	31(5)
H(21A)	9523	4184	8752	32
H(21B)	7722	3712	8369	32
H(21C)	10550	3792	8278	32

Table 6. Torsion angles [°] for 3.38.

O(20)-C(1)-C(2)-C(3)	178.44(9)
C(21)-C(1)-C(2)-C(3)	-62.86(14)
C(12)-C(1)-C(2)-C(3)	61.75(13)
C(1)-C(2)-C(3)-C(4)	179.67(10)
C(2)-C(3)-C(4)-O(19)	-174.74(10)
C(2)-C(3)-C(4)-C(5)	61.01(14)
O(19)-C(4)-C(5)-C(6)	-66.46(12)
C(3)-C(4)-C(5)-C(6)	58.04(13)
C(4)-C(5)-C(6)-O(18)	45.99(15)
C(4)-C(5)-C(6)-O(7)	-131.72(10)
O(18)-C(6)-O(7)-C(8)	-4.06(17)
C(5)-C(6)-O(7)-C(8)	173.63(9)
C(6)-O(7)-C(8)-C(9)	-118.15(11)
O(7)-C(8)-C(9)-C(10)	55.48(13)
O(7)-C(8)-C(9)-C(17)	177.17(9)
C(8)-C(9)-C(10)-C(11)	-116.88(13)
C(17)-C(9)-C(10)-C(11)	123.46(13)
C(9)-C(10)-C(11)-C(12)	175.29(11)
C(10)-C(11)-C(12)-O(13)	118.24(12)
C(10)-C(11)-C(12)-C(1)	-124.95(12)
O(20)-C(1)-C(12)-O(13)	54.68(11)
C(21)-C(1)-C(12)-O(13)	-66.09(12)
C(2)-C(1)-C(12)-O(13)	168.41(9)
O(20)-C(1)-C(12)-C(11)	-63.76(12)
C(21)-C(1)-C(12)-C(11)	175.46(10)
C(2)-C(1)-C(12)-C(11)	49.96(13)
C(11)-C(12)-O(13)-C(14)	-115.67(11)
C(1)-C(12)-O(13)-C(14)	121.54(11)
C(12)-O(13)-C(14)-O(15)	1.77(17)
C(12)-O(13)-C(14)-C(16)	-178.73(10)

Symmetri transformations used to generate equivalent atoms.

Table 7. Hydrogen bonds for 3.38 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(20)-H(20)...O(15)#1	0.790(19)	2.178(19)	2.8910(13)	150.3(17)
O(19)-H(19)...O(18)	0.863(19)	2.077(19)	2.7978(14)	140.5(16)

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z

9 Appendix B – X-ray structure of 5.122

Contents:

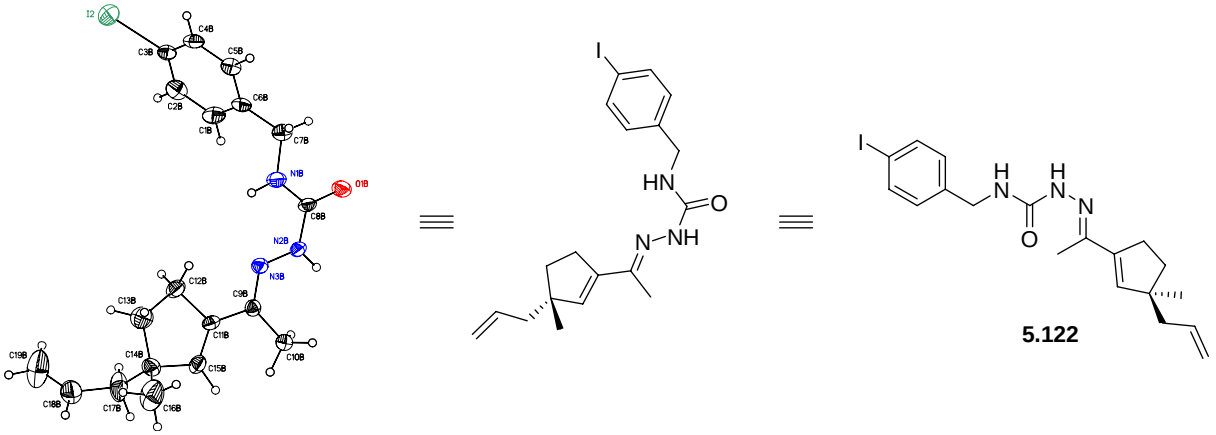


Table 1. Crystal data and structure refinement for 5.122 (CCDC 686849).

Empirical formula	$C_{19}H_{24}N_3OI$
Formula weight	437.31
Crystallization Solvent	Dichloromethane/pentane
Crystal Habit	Needle
Crystal size	0.28 x 0.11 x 0.07 mm^3
Crystal color	Colorless

Data Collection

Type of diffractometer	Bruker KAPPA APEX II
Wavelength	0.71073 Å MoKα
Data Collection Temperature	100(2) K
θ range for 9911 reflections used in lattice determination	2.57 to 28.78°
Unit cell dimensions	a = 17.160(4) Å b = 5.5921(14) Å β= 90.689(6)° c = 19.984(5) Å
Volume	1917.6(8) $Å^3$
Z	4
Crystal system	Monoclinic
Space group	$P2_1$
Density (calculated)	1.515 Mg/m^3
F(000)	880
Data collection program	Bruker APEX2 v2.1-0
θ range for data collection	1.55 to 29.84°
Completeness to θ = 29.84°	88.9 %
Index ranges	$-23 \le h \le 23$, $-7 \le k \le 7$, $-26 \le l \le 25$
Data collection scan type	ω scans; 16 settings
Data reduction program	Bruker SAINT-Plus v7.34A
Reflections collected	8962
Independent reflections	8962 [R_{int}= 0.0000]
Absorption coefficient	1.680 mm^{-1}
Absorption correction	Semi-empirical from equivalents (TWNABS)
Max. and min. transmission	0.7460 and 0.5010

Table 1 (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Geometric positions
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	8962 / 1 / 437
Treatment of hydrogen atoms	Riding
Goodness-of-fit on F^2	1.609
Final R indices [I>2σ(I), 7203 reflections]	R1 = 0.0409, *w*R2 = 0.0481
R indices (all data)	R1 = 0.0619, *w*R2 = 0.0493
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.002
Average shift/error	0.000
Absolute structure determination	Anomalous differences
Absolute structure parameter	0.003(11)
Largest diff. peak and hole	0.807 and -0.967 e.Å^{-3}

Special Refinement Details

The structure was refined as a single component, although the crystals were twins, using an HKLF4 format reflection file prepared with TWINABS (see below). The two orientations were separated using CELL_NOW as follows.

Rotated from first domain by 178.9 degrees about reciprocal axis -0.032 1.000 0.104 and real axis -0.001 1.000 0.007. Twin law to convert hkl from first to this domain (SHELXL TWIN matrix):

```
-1.000  -0.065   0.016
-0.003   0.998   0.014
-0.022   0.207  -0.999
```

From Saint integration; Twin Law, Sample 1 of 1 transforms h1.1(1)->h1.2(2)

```
-0.99897 -0.07583  0.01646
-0.00750  0.99693  0.01538
-0.02464  0.19596 -0.99910
```

Twinabs;

```
PART 1 - Refinement of parameters to model systematic errors

18757 data (   4443 unique ) involve domain  1 only,  mean I/sigma  13.7
18551 data (   4364 unique ) involve domain  2 only,  mean I/sigma   7.1
10342 data (   4106 unique ) involve   2 domains,  mean I/sigma  19.2

HKLF 4 dataset constructed from all observations involving domains 1..2
   8970 Corrected reflections written to file twin4.hkl
 Reflections merged according to point-group 2
 Minimum and maximum apparent transmission:  0.501007  0.745969
 Additional spherical absorption correction applied with mu*r =  0.2000
```

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

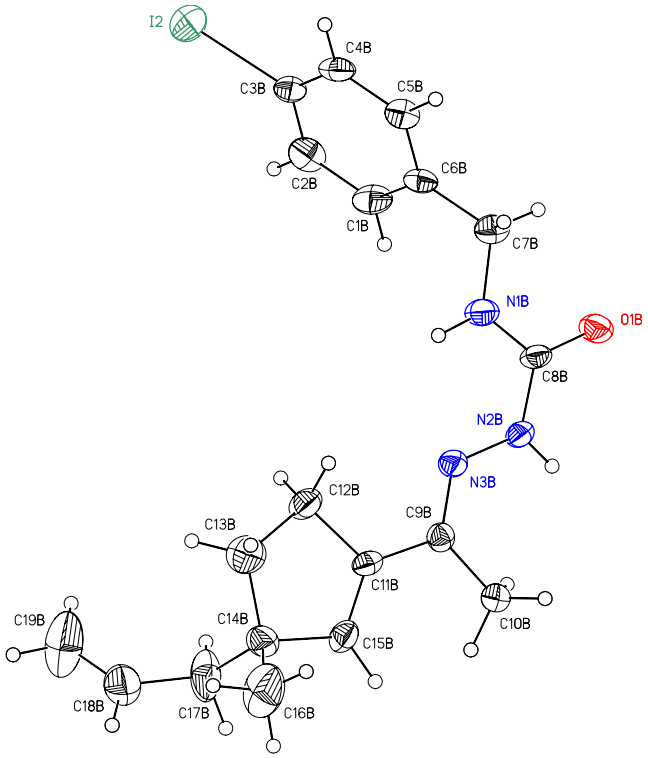

I2
C4B
C3B
C5B
C2B
C6B
C1B
C7B
N1B
O1B
C8B
N2B
N3B
C12B
C9B
C13B
C11B
C10B
C19B
C14B
C15B
C18B
C17B
C16B

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 5.122 (CCDC 686849). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
I(1)	9525(1)	8297(1)	6590(1)	36(1)
O(1A)	7955(1)	941(3)	3051(1)	30(1)
N(1A)	7500(2)	3872(4)	3727(1)	30(1)
N(2A)	6670(2)	1070(4)	3270(1)	28(1)
N(3A)	6059(2)	2296(4)	3562(1)	28(1)
C(1A)	8489(2)	4383(5)	4938(2)	26(1)
C(2A)	8786(2)	5006(6)	5555(2)	27(1)
C(3A)	9158(2)	7186(5)	5637(2)	24(1)
C(4A)	9240(2)	8700(6)	5094(2)	23(1)
C(5A)	8934(2)	8049(6)	4481(2)	24(1)
C(6A)	8541(2)	5886(5)	4389(2)	21(1)
C(7A)	8214(2)	5251(6)	3716(2)	29(1)
C(8A)	7411(2)	1915(5)	3335(2)	24(1)
C(9A)	5356(2)	1676(5)	3411(2)	25(1)
C(10A)	5153(2)	-221(5)	2912(2)	34(1)
C(11A)	4738(2)	3016(6)	3736(2)	25(1)
C(12A)	4902(2)	5012(5)	4229(2)	30(1)
C(13A)	4096(2)	6199(5)	4302(2)	34(1)
C(14A)	3501(2)	4222(5)	4130(2)	33(1)
C(15A)	3985(2)	2625(5)	3693(2)	32(1)
C(16A)	3271(2)	2838(6)	4771(2)	47(1)
C(17A)	2751(2)	5160(6)	3793(2)	36(1)
C(18A)	2864(2)	6198(6)	3116(2)	39(1)
C(19A)	2612(2)	8233(8)	2900(2)	51(1)
I(2)	5760(1)	351(1)	-1541(1)	52(1)
O(1B)	6661(1)	7118(3)	2275(1)	34(1)
N(1B)	7173(2)	4167(4)	1625(1)	34(1)
N(2B)	7955(2)	7040(4)	2098(1)	27(1)
N(3B)	8578(2)	5882(4)	1807(1)	26(1)
C(1B)	6496(2)	3858(5)	289(2)	33(1)
C(2B)	6341(2)	3322(8)	-374(2)	35(1)
C(3B)	5958(2)	1240(6)	-534(2)	29(1)
C(4B)	5742(2)	-303(6)	-40(2)	31(1)
C(5B)	5895(2)	235(6)	618(2)	28(1)
C(6B)	6287(2)	2329(5)	795(2)	26(1)
C(7B)	6454(2)	2863(6)	1519(2)	32(1)
C(8B)	7233(2)	6143(5)	2016(2)	25(1)
C(9B)	9266(2)	6619(5)	1925(2)	24(1)
C(10B)	9471(2)	8670(6)	2382(2)	33(1)
C(11B)	9892(2)	5325(6)	1586(2)	25(1)
C(12B)	9704(2)	3469(7)	1051(2)	34(1)
C(13B)	10499(2)	2401(6)	903(2)	54(1)
C(14B)	11131(2)	4019(5)	1204(2)	33(1)
C(15B)	10659(2)	5558(6)	1666(2)	30(1)
C(16B)	11736(3)	2543(7)	1600(2)	67(2)
C(17B)	11522(2)	5571(7)	690(2)	58(1)
C(18B)	12017(3)	4302(6)	194(2)	52(1)
C(19B)	11859(3)	3982(7)	-416(2)	77(2

Table 3. Bond lengths [Å] and angles [°] for 5.122 (CCDC 686849).

I(1)-C(3A)	2.092(3)	C(9A)-N(3A)-N(2A)	118.6(3)
O(1A)-C(8A)	1.226(4)	C(2A)-C(1A)-C(6A)	122.1(3)
N(1A)-C(8A)	1.354(4)	C(1A)-C(2A)-C(3A)	119.6(3)
N(1A)-C(7A)	1.449(4)	C(2A)-C(3A)-C(4A)	119.8(3)
N(2A)-C(8A)	1.361(4)	C(2A)-C(3A)-I(1)	120.1(2)
N(2A)-N(3A)	1.388(3)	C(4A)-C(3A)-I(1)	119.9(2)
N(3A)-C(9A)	1.289(4)	C(5A)-C(4A)-C(3A)	119.7(3)
C(1A)-C(2A)	1.375(5)	C(4A)-C(5A)-C(6A)	121.7(3)
C(1A)-C(6A)	1.386(4)	C(1A)-C(6A)-C(5A)	117.2(3)
C(2A)-C(3A)	1.385(4)	C(1A)-C(6A)-C(7A)	122.8(3)
C(3A)-C(4A)	1.384(4)	C(5A)-C(6A)-C(7A)	120.1(3)
C(4A)-C(5A)	1.376(4)	N(1A)-C(7A)-C(6A)	115.0(3)
C(5A)-C(6A)	1.397(5)	O(1A)-C(8A)-N(1A)	123.1(3)
C(6A)-C(7A)	1.494(4)	O(1A)-C(8A)-N(2A)	121.2(3)
C(9A)-C(11A)	1.457(4)	N(1A)-C(8A)-N(2A)	115.8(3)
C(9A)-C(10A)	1.494(4)	N(3A)-C(9A)-C(11A)	116.2(3)
C(11A)-C(15A)	1.312(4)	N(3A)-C(9A)-C(10A)	123.9(3)
C(11A)-C(12A)	1.514(5)	C(11A)-C(9A)-C(10A)	119.8(3)
C(12A)-C(13A)	1.542(4)	C(15A)-C(11A)-C(9A)	127.4(3)
C(13A)-C(14A)	1.542(5)	C(15A)-C(11A)-C(12A)	109.9(3)
C(14A)-C(15A)	1.505(4)	C(9A)-C(11A)-C(12A)	122.6(3)
C(14A)-C(17A)	1.538(5)	C(11A)-C(12A)-C(13A)	102.6(3)
C(14A)-C(16A)	1.552(5)	C(12A)-C(13A)-C(14A)	105.2(2)
C(17A)-C(18A)	1.487(5)	C(15A)-C(14A)-C(17A)	114.4(3)
C(18A)-C(19A)	1.290(5)	C(15A)-C(14A)-C(13A)	100.7(3)
I(2)-C(3B)	2.096(3)	C(17A)-C(14A)-C(13A)	113.7(3)
O(1B)-C(8B)	1.242(4)	C(15A)-C(14A)-C(16A)	109.3(3)
N(1B)-C(8B)	1.356(4)	C(17A)-C(14A)-C(16A)	108.2(3)
N(1B)-C(7B)	1.447(4)	C(13A)-C(14A)-C(16A)	110.3(3)
N(2B)-C(8B)	1.346(4)	C(11A)-C(15A)-C(14A)	114.4(3)
N(2B)-N(3B)	1.383(3)	C(18A)-C(17A)-C(14A)	114.4(3)
N(3B)-C(9B)	1.270(4)	C(19A)-C(18A)-C(17A)	127.0(3)
C(1B)-C(6B)	1.376(4)	C(8B)-N(1B)-C(7B)	123.6(3)
C(1B)-C(2B)	1.380(5)	C(8B)-N(2B)-N(3B)	119.3(3)
C(2B)-C(3B)	1.373(5)	C(9B)-N(3B)-N(2B)	119.4(3)
C(3B)-C(4B)	1.366(4)	C(6B)-C(1B)-C(2B)	121.4(3)
C(4B)-C(5B)	1.372(4)	C(3B)-C(2B)-C(1B)	119.6(3)
C(5B)-C(6B)	1.394(5)	C(4B)-C(3B)-C(2B)	120.0(3)
C(6B)-C(7B)	1.501(5)	C(4B)-C(3B)-I(2)	120.1(3)
C(9B)-C(11B)	1.467(4)	C(2B)-C(3B)-I(2)	119.8(2)
C(9B)-C(10B)	1.504(4)	C(3B)-C(4B)-C(5B)	120.3(3)
C(11B)-C(15B)	1.330(4)	C(4B)-C(5B)-C(6B)	120.9(3)
C(11B)-C(12B)	1.522(4)	C(1B)-C(6B)-C(5B)	117.7(3)
C(12B)-C(13B)	1.521(5)	C(1B)-C(6B)-C(7B)	122.4(3)
C(13B)-C(14B)	1.530(5)	C(5B)-C(6B)-C(7B)	119.8(3)
C(14B)-C(15B)	1.505(4)	N(1B)-C(7B)-C(6B)	113.3(3)
C(14B)-C(17B)	1.509(5)	O(1B)-C(8B)-N(2B)	121.1(3)
C(14B)-C(16B)	1.537(6)	O(1B)-C(8B)-N(1B)	123.0(3)
C(17B)-C(18B)	1.493(5)	N(2B)-C(8B)-N(1B)	115.9(3)
C(18B)-C(19B)	1.260(5)	N(3B)-C(9B)-C(11B)	116.0(3)
C(8A)-N(1A)-C(7A)	120.7(3)	N(3B)-C(9B)-C(10B)	124.7(3)
C(8A)-N(2A)-N(3A)	119.8(3)	C(11B)-C(9B)-C(10B)	119.3(3)

C(15B)-C(11B)-C(9B)	128.7(3)	C(17B)-C(14B)-C(13B)	112.9(3)
C(15B)-C(11B)-C(12B)	110.6(3)	C(15B)-C(14B)-C(16B)	110.9(3)
C(9B)-C(11B)-C(12B)	120.7(3)	C(17B)-C(14B)-C(16B)	110.8(3)
C(13B)-C(12B)-C(11B)	102.9(3)	C(13B)-C(14B)-C(16B)	110.9(3)
C(12B)-C(13B)-C(14B)	108.9(3)	C(11B)-C(15B)-C(14B)	114.2(3)
C(15B)-C(14B)-C(17B)	109.6(3)	C(18B)-C(17B)-C(14B)	116.1(3)
C(15B)-C(14B)-C(13B)	101.3(3)	C(19B)-C(18B)-C(17B)	126.3(5)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^4$) for 5.122 (CCDC 686849). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	340(2)	433(1)	310(1)	1(1)	-116(1)	-2(1)
O(1A)	177(14)	294(13)	431(15)	-131(10)	-15(11)	35(10)
N(1A)	166(17)	377(19)	352(17)	-168(12)	3(13)	-6(12)
N(2A)	150(17)	315(15)	378(18)	-133(12)	-22(13)	22(12)
N(3A)	186(19)	310(15)	328(18)	-35(12)	-35(15)	38(13)
C(1A)	190(20)	176(16)	420(20)	13(15)	-22(18)	9(13)
C(2A)	250(20)	237(18)	320(20)	88(15)	-7(16)	-4(16)
C(3A)	170(20)	261(17)	270(20)	-18(14)	-7(16)	69(14)
C(4A)	180(20)	200(20)	310(20)	-23(14)	-29(15)	-13(14)
C(5A)	240(20)	201(19)	275(19)	26(16)	5(15)	34(16)
C(6A)	171(19)	195(18)	269(19)	-26(14)	-8(15)	64(14)
C(7A)	260(20)	280(18)	330(20)	-40(17)	-16(16)	-38(18)
C(8A)	200(20)	257(18)	260(20)	-33(14)	-61(17)	19(16)
C(9A)	200(20)	231(17)	330(20)	-9(14)	-9(18)	-26(15)
C(10A)	200(20)	410(20)	430(20)	-69(17)	3(18)	-44(17)
C(11A)	190(20)	240(20)	330(20)	21(16)	-31(15)	-26(17)
C(12A)	250(20)	283(18)	360(20)	-23(16)	-60(16)	-30(16)
C(13A)	260(20)	305(19)	440(20)	-99(15)	-50(18)	42(16)
C(14A)	190(20)	305(19)	490(30)	-7(15)	9(19)	19(15)
C(15A)	260(20)	240(20)	460(20)	-48(14)	-26(19)	-18(15)
C(16A)	360(30)	500(30)	540(30)	114(18)	30(20)	88(19)
C(17A)	250(20)	390(20)	450(20)	-34(18)	9(18)	40(20)
C(18A)	270(20)	480(20)	420(30)	-75(18)	-70(20)	77(18)
C(19A)	410(30)	600(20)	510(20)	40(20)	-88(19)	120(30)
I(2)	431(2)	791(2)	333(2)	-69(1)	-57(1)	-30(2)
O(1B)	227(16)	346(12)	447(16)	-105(10)	2(13)	9(11)
N(1B)	220(19)	350(17)	440(20)	-151(12)	-38(16)	9(12)
N(2B)	230(20)	301(15)	272(17)	-106(12)	-29(14)	3(13)
N(3B)	208(18)	309(16)	277(16)	-57(12)	-23(14)	26(14)
C(1B)	340(30)	190(20)	470(30)	-9(15)	-50(20)	-62(15)
C(2B)	310(20)	404(19)	350(20)	130(20)	-22(16)	20(20)
C(3B)	190(20)	370(20)	310(20)	-17(16)	-51(17)	17(16)
C(4B)	200(20)	270(20)	450(30)	-58(16)	-50(18)	-39(15)
C(5B)	270(20)	236(18)	340(20)	71(16)	-20(16)	-10(17)
C(6B)	170(20)	246(18)	350(20)	8(15)	-46(17)	-2(14)
C(7B)	300(20)	310(20)	360(20)	-12(15)	-23(17)	-59(16)
C(8B)	200(20)	282(19)	270(20)	-34(14)	-76(16)	-6(16)
C(9B)	250(20)	257(18)	220(20)	11(14)	2(17)	11(16)
C(10B)	260(20)	400(20)	330(20)	-104(16)	37(16)	-60(18)

C(11B)	250(20)	241(17)	253(19)	-25(16)	-45(15)	-52(18)
C(12B)	340(20)	341(18)	330(20)	-105(19)	-60(16)	10(20)
C(13B)	450(30)	450(20)	730(30)	-310(20)	70(30)	-4(19)
C(14B)	250(20)	350(20)	390(20)	-54(15)	20(19)	25(15)
C(15B)	340(20)	290(18)	266(19)	-75(16)	-25(16)	33(18)
C(16B)	720(40)	680(30)	610(30)	-170(20)	-50(30)	380(30)
C(17B)	840(30)	400(20)	510(30)	-150(20)	330(20)	-90(20)
C(18B)	500(30)	540(30)	520(30)	-104(19)	110(30)	-49(19)
C(19B)	1060(50)	830(40)	420(30)	40(20)	60(30)	500(30)

Table 5. Hydrogen bonds for 5.122 (CCDC 686849) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2A)-H(2A)...O(1B)#1	0.88	2.13	2.972(3)	159.7
N(2B)-H(2B)...O(1A)#2	0.88	2.04	2.895(3)	163.1

Symmetry transformations used to generate equivalent atoms:
#1 x,y-1,z
#2 x,y+1,z

10 Appendix C Publications

1) *"Synthesis of the Macrocyclic Core of (–)-Pladienolide B"* Philip R. Skaanderup and Thomas Jensen *Org. Lett.* **2008**, *10*, 2821.

2) *"Ruthenium-Catalyzed Alkylation of Oxindole with Alcohols"* Thomas Jensen and Robert Madsen *J. Org. Chem* **2009**, *74*, 3990.

ORGANIC LETTERS

2008
Vol. 10, No. 13
2821−2824

Synthesis of the Macrocyclic Core of (−)-Pladienolide B

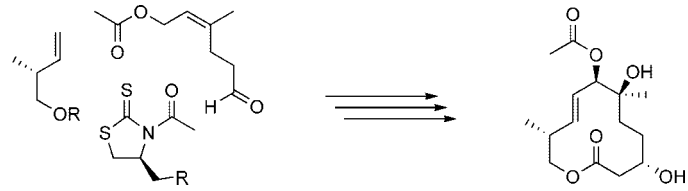
Philip R. Skaanderup*,†,‡ and Thomas Jensen†

Department of Chemistry, Technical University of Denmark, Building 201, Kemitorvet, DK-2800 Kgs. Lyngby, Denmark, and Novartis Institutes for BioMedical Research, Novartis AG, CH-4056 Basel, Switzerland

philip.skaanderup@novartis.com

Received April 24, 2008

ABSTRACT



An efficient synthesis of the macrocyclic core of (−)-pladienolide B is disclosed. The concise route relies on a chiral auxiliary-mediated asymmetric aldol addition and an osmium-catalyzed asymmetric dihydroxylation to install the three oxygenated stereocenters of the macrocycle. This purely reagent-controlled and flexible strategy sets the stage for future analogue syntheses and structure−activity relationship plotting of the appealing anticancer lead structure pladienolide B.

The identification of new targets of clinical relevance is a cornerstone in improving the level of existing disease remedies and for developing new therapies for hitherto untreatable diseases.[1] Recently, it has been indicated that splicing factors are important potential targets for the development of new cancer therapies.[2] The natural product pladienolide B (**1**, Figure 1) potently inhibits cancer cell proliferation, and biological studies aimed at elucidating its mode of action have led to a proposed mechanism involving binding to the splicing factor SF3b.[3] Pladienolide B was isolated by Sakai and co-workers in 2004 from the fermentation broth of *Streptomyces platensis* Mer-11107 using a screen designed to identify compounds that inhibit cell signaling pathways in a tumor-specific microenvironment.[4a–c] Significantly, pladienolide B inhibts hypoxia-induced VEGF expression and proliferation of human cancer cell lines with low to subnanomolar IC_{50} values.[4a,c] Moreover, pladienolide B displays unchanged inhibitory activity against drug-resistant cancer cells, as compared to their parental cell lines, and has demonstrated complete regression of BSY-1 tumors in xenograft mice models.[4c] This unique biological profile has inspired considerable interest from the scientific community[5,6] leading to elucidation of the absolute stereochemistry[5] (**1**, Figure 1) and the first total synthesis by Kotake and co-workers.[6a,c] Despite these noteworthy efforts, little is known about the structural basis for pladienolide B's modulation of spliceosomal activity and potential interaction with other targets.

At the outset of our synthetic efforts in April 2005, only the planar structure of pladienolide B had been reported.[4b,7] Interestingly, the 12-membered core and the side chain of pladienolide B resemble the macrocyclic core of 10-

† Technical University of Denmark.
‡ Novartis Institutes for BioMedical Research.

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10.1021/ol800946x CCC: $40.75
Published on Web 05/30/2008

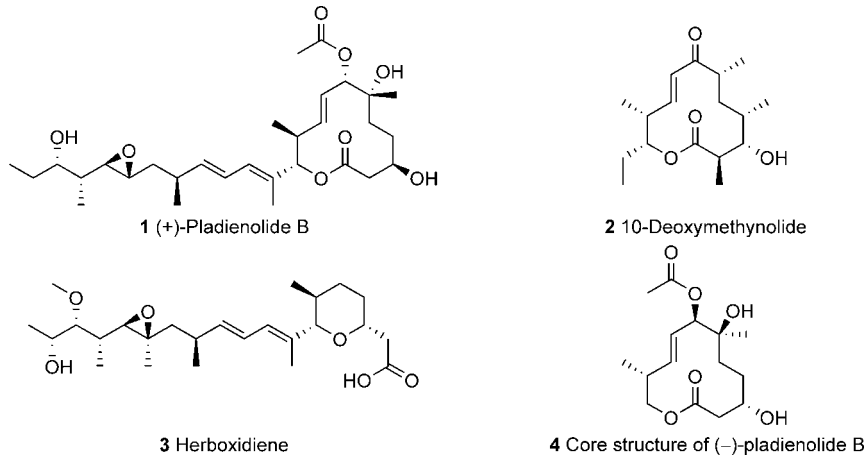
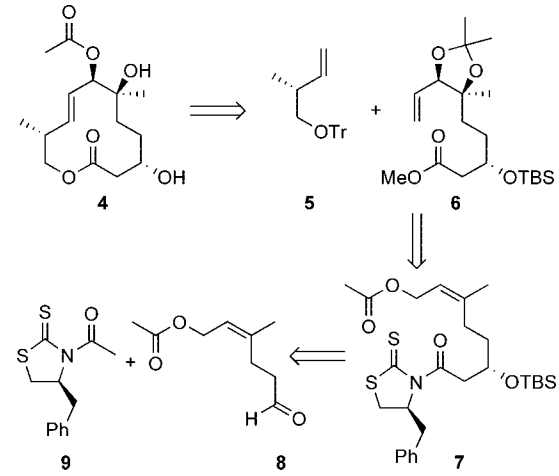


Figure 1. Metabolites of the *Streptomyces* family **1**−**3** and target structure **4**.

deoxymethynolide[8] (**2**, Figure 1) and the side chain of herboxidiene[9] (**3**). From an evolutionary point of view, it is conceivable that pladienolide B and other secondary metabolites produced by *Streptomyces* strains, such as herboxidiene and 10-deoxymethynolide, could be synthesized by polyketide synthases encoded by related gene clusters.[10] Consistent with a common biogenesis for these three polyketides, we projected that the absolute configuration of **1** would correlate to that of **2** and **3**. Hence, we focused our synthetic studies on the asymmetric synthesis of core structure **4**, the enantiomer of the (+)-pladienolide B core (Figure 1). Herein, we wish to report a convergent synthesis of **4** and its crystal structure.

Structurally, the core structure **4** consists of a 12-membered macrolactone bearing four stereocenters with an *O*-acetylated secondary alcohol adjacent to a tertiary hydroxyl group. The macrolactone also contains a disubstituted trans olefin, a tertiary stereocenter, and a second hydroxyl group stereocenter. Toward our synthetic target **4** we envisioned a strategy with maximum flexibility that would provide access to all sixteen stereoisomers of the core structure. Specifically, we envisioned an orthoester formation and ring-opening sequence to selectively acetylate the desired secondary alcohol and complete the synthesis of **4**. Macrolactonization and (*E*)-selective cross metathesis between olefins **5** and **6** could construct the 12-membered lactone. **5** would in turn be available from commercial (*S*)-Roche ester and **6** was anticipated to arrive from sequential olefination and osmium-catalyzed asymmetric dihydroxylation thereby installing the vicinal oxygen-substituted stereocenters of the macrocycle. Finally, key intermediate **7** would result from chiral auxiliary-mediated asymmetric aldol addition of known acetylthiazolidine-thione **9** and aldehyde **8** (Scheme 1).

Scheme 1. Retrosynthesis of (−)-Pladienolide B Core Structure



The synthesis takes advantage of the easily obtainable building blocks **5** and **8** (Scheme 2). Tritylation of (*S*)-Roche ester **10** followed by LAH reduction, Swern oxidation,[11] and Wittig methylenation afforded alkene **5** smoothly over this four-step sequence (Scheme 2a). Prilezhaev epoxidation[12] of commercial acetate **11** and subsequent epoxide cleavage

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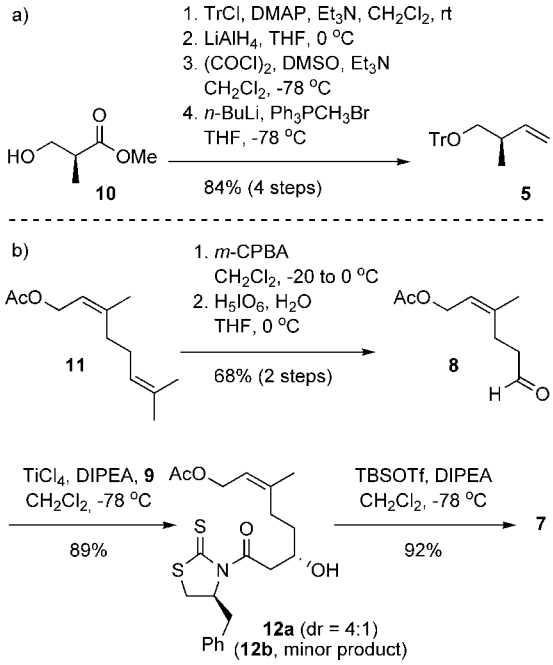
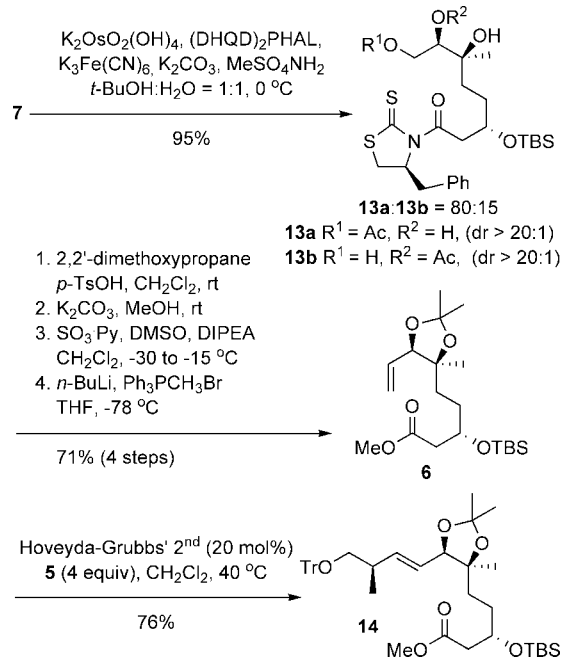
Scheme 2. Synthesis of Intermediates **5**, **8**, and **7**



Scheme 3. Synthesis of (*E*)-Olefin **14**



using periodic acid provided aldehyde **8**.[13] Secondary alcohol **12a** was available via an asymmetric aldol reaction of aldehyde **8** with a chiral acetylthiazolidinethione enolate generated from **9** using Vilarrasa's conditions.[14] The selectivity of the aldol reaction could be tuned to give either **12a** or **12b** as the major product even when the same acetylthiazolidinethione was employed. The titanium enolate generated with titanium tetrachloride and Hünig's base gave predominantly the desired isomer **12a** in excellent yield. If the enolate was generated from dichlorophenylborane and (−)-sparteine, **12b** was formed as the major product.[15] Additionally, the valine and *tert*-leucine-derived auxiliaries gave slightly improved product ratios of 5:1 to 6:1. However, we chose to use the phenylalanine-derived auxiliary because all intermediates leading to **9** are crystalline and can be obtained easily in analytically pure form. The aldol product was then protected as the TBS ether to give **7** in 92% yield (Scheme 2b).

The oxygenated functionality at the northern portion of the target molecule was installed by Sharpless's asymmetric dihydroxylation protocol.[16] From the well-defined olefin geometry of the substrate, which relates back to nerol and using the $(DHQD)_2PHAL$ ligand, diol **13a** was produced in good yield and selectivity greater than 20:1 at the newly formed stereocenters (Scheme 3). Acetate **13b** was also formed in equal diastereomeric ratio and is the likely product of intramolecular acetyl migration. All attempts to convert **13b** into **13a** were unsuccessful. The key alkene fragment **6** was prepared from **13a** in a four-step sequence initially involving acetonide formation and treatment with K_2CO_3 in methanol to concomitantly cleave the acetate and convert the chiral auxiliary into a methyl ester.[17] Parikh−Döering oxidation[18] followed by Wittig methylenation provided alkene **6** in 71% yield over these four steps. With compound **6** in hand, we set out to identify reaction conditions that would furnish (*E*)-alkene **14** efficiently. Initial attempts to mediate the cross-metathesis between olefins **5** and **6** with 10 mol% of either Grubbs' second-generation catalyst,[19] Hoveyda−Grubbs' second-generation catalyst,[20] or Grubbs' third-generation catalyst[21] gave the desired alkene **14** in less than 30% yield.[22] Interestingly, only the (*E*)-alkene was observed by ^1H NMR. Following optimization the yield of **14** could be improved to 76% using Hoveyda−Grubbs' second-generation catalyst and by adding **5** in two portions over the course of the reaction (Scheme 3). Selective deprotection of the trityl ether using a solution of BCl_3[23] followed by methyl ester hydrolysis successfully gave *seco*-acid **15** in 84% yield for this two-step sequence (Scheme 4).

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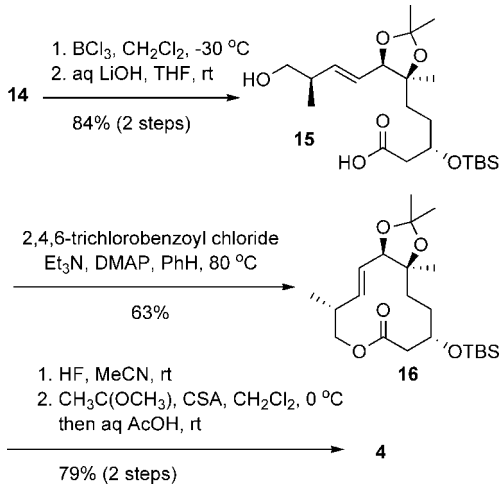
(22) Using the corresponding TBS-ether afforded the desired alkene in 25% yield; however, the TBS-ether was volatile and thus impractical to employ in the synthesis.

Scheme 4. Macrolactonization and Completion of **4**



Attempts to close the macrocycle under modified Yamaguchi conditions[24] at room temperature produced **16** in 34% yield. However, by increasing the reaction temperature to 80 °C and adding the preformed mixed anhydride slowly to a DMAP-benzene solution,[25] the yield improved considerably, and macrocycle **16** could be isolated in 63% yield. The TBS and acetonide groups were then effectively removed through the action of aqueous HF in MeCN.[26] Finally, the secondary allylic alcohol was acetylated selectively by treating the diol with trimethyl orthoacetate and CSA followed by cleavage of the resulting orthoester with aqueous AcOH to give the macrocyclic core structure **4** in 86% yield (Scheme 4).

The structure and absolute stereochemistry of macrolactone **4** were unambiguously established by single-crystal X-ray crystallography (Figure 2).[27]

In summary, the macrocyclic core of (−)-pladienolide B (**4**) has been synthesized in 8.1% overall yield starting from

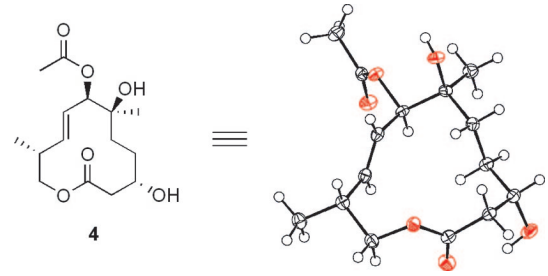


Figure 2. Structure of **4** in the crystal.[28] The ellipsoids are drawn at the 50% probability level, and the hydrogen atoms are drawn with an arbitrary radius. For the enantiomer shown, the Flack *x* parameter refined to 0.03(4).[29]

10 and **11** using a total number of 19 steps (longest linear = 15 steps). The achieved synthesis, with full control of all four stereocenters of the macrocyclic core structure, illustrates the flexibility of our approach. Through cross metathesis reactions between olefin **6** and homoallylic alcohols, as a readily available source of chemical diversity, our method sets the stage for rapid synthesis of new pladienolide analogues.[30] Our ongoing efforts are focused on using this strategy to synthesize new side-chain analogues and to study the structural basis for pladienolide B's anticancer activity.

Acknowledgment. This work was supported by The Danish Research Council for Technology and Production Sciences, grant no. 26-04-0143. We gratefully acknowledge Trixie Wagner (Novartis AG, Switzerland) for the X-ray structure determination and Professor Robert Madsen (Technical University of Denmark) for helpful discussions.

Supporting Information Available: Full experimental details and spectral data for all new compounds. This material is availabe free of charge via the Internet at http://pubs.acs.org.

OL800946X

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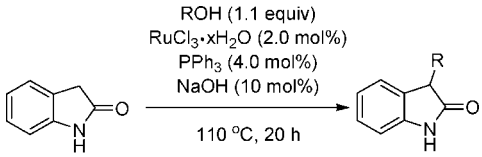
Ruthenium-Catalyzed Alkylation of Oxindole with Alcohols

Thomas Jensen and Robert Madsen*

Department of Chemistry, Building 201, Technical University of Denmark, DK-2800 Lyngby, Denmark

rm@kemi.dtu.dk

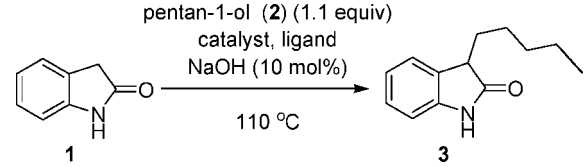
Received February 16, 2009



An atom-economical and solvent-free catalytic procedure for the mono-3-alkylation of oxindole with alcohols is described. The reaction is mediated by the in situ generated catalyst from $RuCl_3 \cdot xH_2O$ and PPh_3 in the presence of sodium hydroxide. The reactions proceed in good to excellent yields with a wide range of aromatic, heteroaromatic, and aliphatic alcohols.

The oxindole ring system is found in many natural products[1] and biologically active molecules.[2] Usually, the 3-position is substituted with one or two substituents which can be introduced from the parent molecule by alkylation with alkyl halides[2]/allylic esters[3] or by arylation with aryl halides.[4] Recently, alcohols have been used for alkylation of activated methylene compounds such as malonates,[5] barbiturates,[6] ketones,[7] and certain nitriles[8] where water is produced as the only byproduct. In all cases, the pK_a value of the methylene group is less than ~20 and the alkylation is achieved with a transition-metal catalyst and a base. The mechanism involves dehydrogenation of the alcohol to the carbonyl compound followed by addition of the activated methylene compound, elimination of water, and hydrogenation of the resulting C−C double bond.[9] Since the pK_a of the methylene group in oxindole is 18.2,[10] we speculated that this environmentally friendly alkylation reaction could also be used for introducing substituents in the 3-position of this motif.[11] Herein, we describe an expedient ruthenium-catalyzed procedure for alkylation of oxindoles with alcohols.

TABLE 1. Catalyst Screening for the Alkylation of Oxindole (1) with Pentan-1-ol (2)[a]



entry	catalyst	catalyst loading (mol %)	ligand	**3**[b] (%)
1	$[Cp^*IrCl_2]_2$	1.0		>95
2	$[IrCl(cod)]_2$	1.0	PPh_3	32[c]
3	$[RuCl_3 \cdot xH_2O]$	2.0	PPh_3	>95[c]
4	$[RuCl_3 \cdot xH_2O]$	2.0		0
5	$[RuCl_2(PPh_3)_3]$	2.0		>95
6	$[Ru(p\text{-cymene})Cl_2]_2$	1.0		47
7	$[Ru(p\text{-cymene})Cl_2]_2$	1.0	Xantphos	>95[d]
8	$[Ru(PPh_3)_3(CO)H_2]$	2.0		53
9	$[Ru(PPh_3)_3(CO)H_2]$	2.0	Xantphos	81[d]
10	Shvo's[14]	1.0		>95
11	$[Ru(acac)_3]$	1.0		0

[a] **1** (2.0 mmol) was reacted with **2** (2.2 mmol) under the influence of catalyst (1.0−2.0 mol %) and NaOH (10 mol %) at 110 °C for 20 h. [b] Conversion was estimated by ^1H NMR spectroscopy based on **1**. [c] PPh_3 (4.0 mol %). [d] Xantphos (2.0 mol %).

The studies began with investigating the direct catalytic alkylation of oxindole (**1**) with pentan-1-ol (**2**) (Table 1). We

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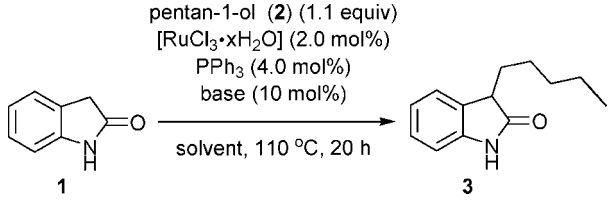
10.1021/jo900341w CCC: $40.75
Published on Web 04/16/2009

TABLE 2. Influence of Base and Solvent on the Catalytic Alkylation of Oxindole (1) with Pentan-1-ol (2)[a]



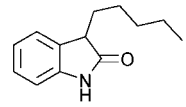
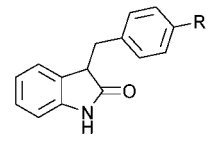
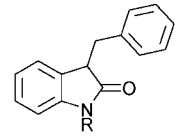
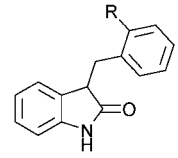
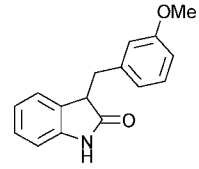
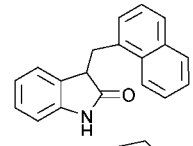
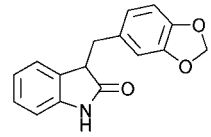
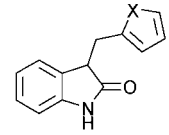
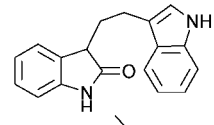
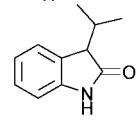
entry	base	solvent	**3**[b] (%)
1	NaOH		>95
2	KOH		>95
3	Na_2CO_3		58
4	K_2CO_3		80
5	Cs_2CO_3		>95
6	Et_3N		39
7			0
8	NaOH	toluene	>95[c]
9	NaOH	*p*-dioxane	92[c]
10	NaOH	water	58[c]

[a] **1** (2.0 mmol) was reacted with **2** (2.2 mmol) under the influence of $RuCl_3 \cdot xH_2O$ (2.0 mol %), PPh_3 (4.0 mol %), and base (10 mol %) at 110 °C for 20 h. [b] Conversion was estimated by ^1H NMR spectroscopy based on **1**. [c] Solvent (1.0 mL) added.

decided to employ the commercially available trivalent iridium complex $[Cp^*IrCl_2]_2$[12] for the first experiments since this catalyst has previously shown high reactivity in the alkylation of barbiturates and arylacetonitriles with primary alcohols.[6,8a] After surveying a small range of bases and reaction temperatures, it was found that the alkylation of **1** with **2** proceeded cleanly to provide the 3-alkylation product in almost quantitative yield when the reaction was performed under neat conditions at 110 °C. Surprisingly, the catalyst system based on $[IrCl(cod)]_2$ and PPh_3 only provided the desired product in low yield (Table 1, entries 1 and 2). With these encouraging results in hand, we decided to examine the performance of a range of different catalysts in the alkylation reaction in order to find a cheaper ruthenium-based catalyst system. The in situ generated catalyst based on $[RuCl_3 \cdot xH_2O]$ and PPh_3 as well as the preformed $[RuCl_2(PPh_3)_3]$ complex afforded the desired product in high yield (entries 3 and 5). The addition of PPh_3 proved to be essential since the absence of PPh_3 resulted in complete recovery of the starting materials. A selection of other ruthenium-based catalysts were tested in the reaction. $[Ru(p\text{-cymene})Cl_2]_2$ and $[Ru(PPh_3)_3(CO)H_2]$ in combination with Xantphos[13] as well as Shvo's catalyst[14] provided the product in high yields while $[Ru(acac)_3]$ and $[Ru(p\text{-cymene})Cl_2]_2$ with no additional ligand added gave either no reaction or low conversion (entries 6−11). We did not in any case observe dialkylation of the C-3-position, nor did we observe any *N*- or *O*-alkylation. Based on this initial screening, we decided to use $[RuCl_3 \cdot xH_2O]$ in combination with PPh_3 for the further studies.

A number of experiments were carried out to investigate the influence of the base and the solvent (Table 2). Sodium hydroxide and potassium hydroxide seemed to perform equally well leading to complete conversion of the starting material (entries 1 and 2). Lower yields were observed when sodium or potassium carbonate as well as triethylamine were employed, while cesium carbonate afforded full conversion of **1** (entries 3−6). Not surprisingly no reaction was observed in the absence of a base, and the starting materials were recovered quantitatively (entry 7). The reaction performed very well in toluene or dioxane while water gave a slightly lower yield (entries 8−10). However, for general use we decided to use sodium hydroxide as the additive under neat reaction conditions.

TABLE 3. Catalytic Alkylation of Oxindole (1) with Various Alcohols[a]

entry	product		yield[b]
1			89
2		R = H	89
3		F	83
4		CF_3	86
5		Cl	89
6		Me	92
7		OMe	83
8		NHPiv	74[c]
9		Bn	91
10		PMB	92
11		F	81
12		Cl	88
13		Me	90
14		OMe	85
15			84
16			87
17			79
18		X = O	71[c]
19		S	81
20			72[c]
21			73[d]

[a] **1** (2.0 mmol) was reacted with **2** (2.2 mmol) under the influence of $RuCl_3 \cdot xH_2O$ (2.0 mol %), PPh_3 (4.0 mol %), and base (10 mol %) at 110 °C for 20 h. [b] Isolated yield. [c] Toluene (1.0 mL) used as cosolvent. [d] Stirred for 48 h with 5 equiv (10 mmol) of the alcohol.

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We then turned our attention to other alcohols in order to investigate the scope of the 3-alkylation procedure (Table 3). The reaction proceeded in high yield when benzylic alcohols with either electron-donating or electron-withdrawing groups present in the 2-, 3-, or 4-position were employed (entries 2−8 and 11−15). It is interesting that chloro substituents are tolerated under the reactions conditions (entries 5 and 12) since they will allow for further functionalization of the alkylated product through cross-coupling chemistry. The use of 4-bromobenzyl alcohol or 4-(hydroxymethyl)benzonitrile led to complex product mixtures probably due to hydrodehalogenation and hydrolysis, respectively. It should be noted that several protecting groups such as amide, benzyl, and *p*-methoxybenzyl were compatible with the reaction conditions (entries 8−10). Some steric hindrance ortho to the benzyl alcohol is well-tolerated (entries 11−14 and 16), while the highly congested 2,4,6-trimethylbenzyl alcohol and 2,6-dimethoxybenzyl alcohol afforded the desired alkylated product in less than 25% yield as judged by ^{1}H NMR. A variety of pharmacophoric functionalities such as catechol, thiophene, furan, and unprotected indole also proved successful in the catalytic alkylation (entries 17−20). Notably, the attempt to alkylate **1** with 2-hydroxymethylfuran under neat conditions mainly led to decomposition while the addition of toluene provided a clean alkylation (entry 18).

The reaction in entry 21 required longer reaction time and excess alcohol (5 equiv) to reach full conversion of the oxindole which shows that secondary alcohols react significantly slower than the corresponding primary alcohols. Attempts to use cyclohexanol and cyclopentanol gave inseparable mixtures of the α,β-unsaturated aldol product and the desired product. Thus for secondary alcohols the reduction of the putative intermediate α,β-unsaturated carbonyl species seems to be the rate-limiting step. When 4-penten-1-ol was employed in the alkylation procedure, a 2:1 mixture of **3** and the corresponding α,β-unsaturated oxindole was obtained in a modest 27% yield.

In conclusion, we have developed a convenient, cheap, and very effective catalytic system for the selective mono 3-alkylation of unprotected and protected oxindoles with a range of aromatic, heteroaromatic, and aliphatic alcohols. This catalytic hydrogen transfer reaction constitutes a highly atom-economical transformation that can be performed under neat conditions and only produces water as the byproduct.

Experimental Section

General Procedure for 3-Alkylation of Oxindole. [$RuCl_3 \cdot xH_2O$] (8.3 mg, 0.04 mmol), PPh_3 (21.0 mg, 0.08 mmol), NaOH (8.0 mg, 0.2 mmol), oxindole (266 mg, 2.0 mmol), and the alcohol (2.2 mmol) were placed in a 7-mL thick-walled screw-cap vial. The vial was purged with Ar and sealed with a screw-cap. The mixture was placed in an aluminum block preheated to 110 °C and stirred for 20 h or until ^{1}H NMR of the crude reaction mixture showed complete consumption of the oxindole. The reaction mixture was allowed to cool to room temperature followed by dilution with CH_2Cl_2 (10 mL). SiO_2 was added, and the suspension was concentrated under reduced pressure to afford a powder that was purified by use of silica gel chromatography (3 × 15 cm SiO_2, 9:1 → 4:1 → 3:7 *n*-hexane/EtOAc).

3-Pentyl-1,3-dihydroindol-2-one (3) (Table 3, entry 1). Isolated yield 89%; colorless oil; R_f = 0.18 (heptane/EtOAc = 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (bs, 1H), 7.26−7.17 (m, 2H), 7.08−6.98 (m, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.48 (t, J = 5.9, 1H), 2.28−1.86 (m, 2H), 1.55−1.16 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 141.6, 129.9, 127.7, 124.1, 122.2, 109.7, 46.1, 31.8, 30.5, 25.4, 22.4, 14.0; IR (neat) 3211, 3094, 3060, 3031, 2955, 2928, 2858, 1701, 1620, 1470, 1338, 1219, 1100, 749 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{21}N_2O$ ([M + H + MeCN]$^+$) 245.1654, found 245.1649.

Acknowledgment. We thank the Danish National Research Foundation for financial support.

Supporting Information Available: General experimental methods, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900341W

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